NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUN PHARMA GLOBAL FZE and SUN PHARMACEUTICAL INDUSTRIES, INC., Plaintiffs/Counterclaim-Defendants, v. LUPID LTD. and LUPIN PHARMACEUTICALS, INC., Defendants/Counterclaim-Plaintiffs.	Civil Action No. 18-2213 (FLW) **OPINION**

WOLFSON, Chief Judge:

Plaintiffs Sun Pharma Global Fze and Sun Pharmaceutical Industries, Inc., manufacture BromSite,[1] the commercial embodiment of U.S. Patent No. 8,778,999 ("the '999 Patent"), which is used to treat and prevent pain associated with cataract surgery.[2] In 2018, Defendants Lupin Ltd. and Lupin Pharmaceuticals, Inc., filed an Abbreviated New Drug Application[3] ("ANDA") with the Federal Drug Administration ("FDA") to market a generic, bioequivalent version of BromSite. Plaintiffs sued for infringement and Defendants counterclaimed, seeking a declaratory judgment that the BromSite patent is invalid because it is obvious, indefinite, and/or unenforceable for inequitable conduct, which Dr. Lyle Bowman allegedly committed during prosecution before the Patent & Trademark Office ("PTO"). I held a five-day remote bench trial in March 2021. Pursuant

1 New Drug Application ("NDA") No. 206911, approved on June 1, 2016. Tr. at 57:2-24 (counsel); PTX No. 023.

2 The '999 Patent was filed on March 5, 2009, issued on July 15, 2014, and expires on August 7, 2029.

3 ANDA No. 211239.

to Fed. R. Civ. P. 52(a), I herein set forth my findings of facts and conclusions of law. After considering the evidence, and based on the trial record, I find that Defendants' ANDA does not literally infringe the '999 Patent; regardless, the '999 Patent is obvious in light of U.S. Patent No. 6,159,458 ("Bowman I")[4] as well as indefinite because it does not specify a critical measurement parameter on spin time; and Dr. Bowman did not commit inequitable conduct before the PTO by not disclosing Bowman I.

I. OVERVIEW

A. The '999 Patent

Plaintiffs own the '999 Patent, pursuant to a March 2016 agreement with Insite Vision Inc., the original assignee, whom they acquired in 2015. PTX Nos. 004-005, 012, 046; Tr. at 50:13-53:15. Named inventors are Drs. Kamran Hosseini, Lyle Bowman, Erwin C. Si, and Stephen Pham. Claim 1 of the '999 Patent has five parts: (i) the active ingredient bromfenac; (ii) a "flowable crosslinked carboxy-containing polycarbophil mucoadhesive polymer" vehicle, colloquially called "polycarbophil"; (iii) a certain pH range; (iv) a certain viscosity range; and a "topical ophthalmic composition." In full, it discloses:

> [a] topical ophthalmic composition formulated for application to the eye, said composition comprising a therapeutically effective amount of bromfenac and a flowable crosslinked carboxy-containing polycarbophil and mucoadhesive polymer, wherein the composition has a viscosity in the range of about 1,000 to about 3,400 cps and a pH of about 7.4 to about 8.5.

Id.

Bromfenac is a non-steroidal anti-inflammatory ("NSAID") first patented in 1990 and approved by the FDA in 2005. DTX Nos. 175, 355, 364; Tr. at 156:13-16, 158:23-159:2 (Bowman); *id.* at 622:9-15, 626:3-635:25 (Hanes). It is indicated for "treatment of postoperative

4 Bowman I was issued to InSite on December 12, 2000. DTX No. 003. It did not result in any commercial product, and InSite "put it aside." Tr. at 200:4-15 (Bowman).

inflammation and prevention of ocular pain in patients undergoing cataract surgery." PTX No. 016. Topical eye drops are the preferred drug delivery method for the eye. Tr. at 373:14-374:4 (Olejnik); *id.* at 554:25-555:21 (Hanes). However, the eye rapidly blinks them away, which limits absorption time and efficacy. *Id.* at 374:5-376:5 (Olejnik); *id.* at 556:22-558:18 (Hanes). A mucoadhesive polymer adheres the drop to preocular tissue for a sustained period, thereby resisting the eye's natural drainage mechanisms and enhancing bioavailability. *Id.* at 128:4-20 (Bowman); *id.* at 376:10-377:3 (Olejnik); *id.* at 558:20-562:10, 598:8-599:21 (Hanes). InSite used proprietary "DuraSite" technology for this purpose, and with it, developed various ophthalmic solutions starting in the 1980s. *See, e.g.*, *id.* at 125:23-126:7 (Bowman); DTX Nos. 25, 251, 942. One of those solutions was AquaSite and another was AzaSite. DTX Nos. 251, 142. By 2008, InSite focused exclusively on "low-risk" projects, or "[e]xisting commercial ophthalmic products enhanced by [the] DuraSite vehicle to outperform the current commercial profile." DTX Nos. 47_68, 129_1, 42_3; Tr. at 170:17-171:13 (Bowman). Chief among them: BromSite, the commercial embodiment of the '999 Patent.

B. Procedural History

Plaintiffs sued Defendants for infringement on February 15, 2018, claiming that Defendants' generic contains a chemically identical bromfenac ophthalmic solution in all the same proportions.[5] Compl., at 2, 7-8. Defendants respond that their generic does not infringe because it has a different viscosity. Defendants also challenge the validity of the '999 Patent on the grounds that it is obvious, indefinite, and that Dr. Bowman, who prosecuted it before the PTO, failed to submit prior art he invented, namely Bowman I. Answer, at 10-11; ECF No. 165, at 2-3.

5 The parties attempted to settle in 2020, ECF No. 145, but were unable to do so. ECF No. 155. The parties also unsuccessfully attempted settlement in 2021 leading up to trial. Time was excluded from the case, and delays permitted, for this reason.

I conducted a five-day bench trial, via Zoom, on March 22-26, 2021. Various fact and expert witnesses testified. For Plaintiffs: Drs. Bowman, Hosseini, Si, and Pham, the latter three by deposition; corporate witness Dr. Bharati Nadkarni, by deposition; and Dr. Orest Olejnik, who I accepted as an expert in "the design and development of ophthalmic pharmaceutical formulations."[6] For Defendants: Dr. Daniel Bloch, who I accepted as an expert in statistical analysis, and Dr. Justin Hanes, who I accepted as an expert in "the fields of pharmaceutical science, drug delivery, and drug design and development, ophthalmic formulation, with specialized expertise in pharmacokinetics and mathematical modeling of the same."

II. INFRINGEMENT

Under 35 U.S.C. § 271(e)(2)(A), an ANDA that describes "a drug claimed in a patent" constitutes an infringing act. *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1377 (Fed. Cir. 2011). "[A]n infringement inquiry provoked by an ANDA filing . . . is focused on a comparison of the asserted patent against 'the product that is likely to be sold following ANDA approval.'" *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1186 (Fed. Cir. 2014) (citation omitted). "In a bench trial," whether the ANDA infringes is a question of fact. *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1125 (Fed. Cir. 2018); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). The patentee must prove by a preponderance of the evidence that every claim limitation found in the patent is also found in the ANDA product, either literally or under the doctrine of equivalents.[7] *Roche Palo Alto LLC v. Apotex, Inc.*, 531 F.3d 1372, 1377

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6 Defendants objected to Dr. Olejnik's opinions on gelation in pretrial motions. ECF No. 185. I reserved ruling on their objection until trial. However, Dr. Olejnik did not testify about gelation-related issues.

7 Plaintiffs do not assert infringement under the latter doctrine. Tr. at 450:11-18 (Olejnik) (stating that he is not offering an opinion on the doctrine of equivalents, only on literal infringement).

(Fed. Cir. 2008); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed. Cir. 2003). "If any claim limitation is absent . . . , there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Rsch. Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000) ("Literal infringement require the patentee to prove that the accused device contains each limitation of the asserted claim(s).").

In the ANDA context, infringement inevitably hinges on minor details of specific claims because the accused generic must be pharmaceutically and therapeutically equivalent to the patented product as a matter of law, 21 U.S.C. § 355(j)(1), yet it cannot be deemed infringing based on the fact of the ANDA alone. *See, e.g.*, *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) ("[A] district court's inquiry in a suit brought under § 271(e)(2) is the same as it is in any other infringement suit . . . . The occurrence of the [statutorily] defined 'act of infringement' does not determine the ultimate question whether what will be sold will infringe any relevant patent."); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990) (observing that § 271(e)(2) "define[s] a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications"). Ultimately, the claims in the patent define the invention, *Autogiro Co. v. United States*, 384 F.2d 391, 395-96 (Ct. Cl. 1967), and they must measure up against each element of the ANDA. *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985).

A. The ANDA

Claim 1 of the '999 Patent discloses five limitations: bromfenac, polycarbophil, a pH range, a viscosity range, and a method of treatment. *Supra*. Except for viscosity, which I will discuss at length *infra*, Defendants' ANDA by its terms meets every limitation in Claim 1. Defendants propose an ophthalmic solution intended for use in the eye, like BromSite. PTX No. 149; Tr. at 386:21-25 (Olejnik) (describing prescribing information for generic, which instructs patients to

"instill one drop, in dosage and administration, . . . of bromfenac ophthalmic solution to the affected eye," in part by tilting the head back and squeezing the bottle, mirroring BromSite's directions). Defendants also propose a bromfenac concentration of 0.075%, the same as BromSite's. PTX No. 020-F. In fact, Defendants' ANDA cross-references clinical data from InSite indicating that 0.075% is a therapeutically effective amount. *Id.*; Tr. at 393:8-9 (Olejnik). Next, BromSite requires a flowable crosslinked carboxy-containing polycarbophil mucoadhesive polymer, or polycarbophil, equal to between 0.5 to 1.5% of the composition's weight. Tr. at 394:6-12 (Olejnik). BromSite specifically contains 0.875% polycarbophil. PTX No. 17-A; Tr. at 394:19-22 (Olejnik). Defendants' generic specifies the same polycarbophil weight. PTX No. 020-F. Finally, Plaintiffs indicate a pH range between 7.4 and 8.5. PTX No. 119. BromSite's pH in particular is 8.3. Tr. at 396:5-6 (Olejnik). Defendants propose an identical pH value for their product. PTX No. 020-F; Tr. at 396:11 (Olejnik) (clarifying that Defendants' product returned the following pH numbers during testing: 8.22, 8.25, 8.17).

That is, Defendants seek to market a topical eye treatment with the same safety profile and efficacy, expected adverse events, preservatives in the same amount, inactive ingredients, drug delivery system, and pH (to the 1/100th) as BromSite, and "there is no difference between [Defendants'] proposed product and BromSite with respect to bromfenac content." Dahibhate Depo. Tr., at 99:23-100:1. The "dosage form, route of administration, indications and usage, active ingredient, strength and labeling . . . for the proposed generic drug product are [likewise] the same as those of [BromSite]." PTX No. 020-A. This establishes infringement on each claimed element, save for viscosity. *Zenith Lab's, Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423 (Fed. Cir. 1994) ("It is error for a court to compare in its infringement analysis the accused product or process

with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent.").

B. Trial Testimony

Dr. Olejnik further explains how Defendants' generic meets each of the above-stated limitations in the '999 Patent. *See, e.g.*, Tr. at 386:5-387:9 (topical ophthalmic composition); *id.* at 389:6-390:15, 392:15-393:23 (bromfenac limitations); *id.* at 394:23-395:14 (polycarbophil limitations); *id.* at 396:7-397:6 (pH limitations); *id.* at 422:1-17 (method of treatment). Defendants do not rebut Dr. Olejnik's testimony or contest any limitation but viscosity. *See, e.g.*, *id.* at 383:22-397:6 (Olejnik); *id.* at 497:10-25, 517:7-21 (Hanes); PTX Nos. 149, 020-F. For instance, Defendants' Senior Vice President Pramod Dahibhate testified that he cannot identify any differences between the composition of his generic and BromSite, stating that "[o]ur composition is the same." Dahibhate Depo. Tr. at 99:23-100:1. Senior Vice President Makarand Avachat acknowledges both a "Q1 match[]" and "Q2 match[]" between Defendants' generic and BromSite. Avachat Depo. Tr. at 77:5-8, 10-11, 15; 78:1-3. Q1 refers to matching components/ingredients, while Q2 refers to matching concentrations/amounts. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) ("The concept of bioequivalence means the body is exposed to the same amount of active pharmaceutical ingredient at the same rate after administration of either an immediate-release or extended-release formulation."). Defendants' expert, Dr. Hanes, omits analysis of any limitation besides viscosity. Tr. at 517:9-21 (Hanes). Defendants' trial motion for a partial finding on infringement, which I reserved until now, concerns viscosity only. *Id.* at 471:4-472:21 (Rule 52(c) Motion). And Defendants devote all of their post-trial briefing on infringement to viscosity. Def. Br., at 7-16.

C. Viscosity

i. Conclusions of Fact

1. Relationship Between Viscosity and Non-Newtonian Thixotropic Fluids

Viscosity is relevant, not only because it is the chief disputed limitation in the '999 Patent, but because it determines in part whether Defendants' generic can be considered pharmaceutically equivalent to BromSite. *See, e.g.*, Avachat Depo. Tr. at 163:3-164:5, 163:25-164:5 (stating that, if the "product viscosity is different than the reference listed drug, it cannot be called as the pharmaceutically equivalent product"). Additionally, as Defendants recognize, "changes in viscosity may affect the product performance" itself, PTX No. 020-E, at 403; PTX No. 020-G, because ocular residence time is largely a function of viscousness.

Viscosity hinges on whether a solution is Newtonian or non-Newtonian. Polycarbophils such as BromSite are non-Newtonian. Tr. at 424:11-14 (Olejnik); *id.* at 214:14-17 (Bowman); *id.* at 503:8-504:1 (Hanes). Non-Newtonian fluids do not have a constant viscosity independent of stress, or an inherent viscousness. Their viscosity instead varies with force and time. *Id.* at 213:16-216:20 (Bowman); *id.* at 424:11-14 (Olejnik) (polycarbophils "would be pseudoplastic, non-Newtonian"); *id.* at 22:4-7. Ketchup and toothpaste are classic examples of non-Newtonian fluids: they become runnier when stirred or shaken. Water is a classic example of a Newtonian fluid: it does not react to any force it experiences. Polycarbophils like BromSite are also thixotropic fluids, which means that their viscosity depends on how long they are exposed to a "shearing force" such as stirring or shaking. *See, e.g.*, *id.* at 502:16-23 (Hanes) ("[A]s you start to shear or stir [solutions] . . . if their viscosity decreases as a function of how long you have been stirring them, then they're called thixotropic."); *id.* at 503:8-22 (Hanes) (confirming that polycarbophils like BromSite exhibit thixotropy). The longer a non-Newtonian thixotropic fluid is exposed to a shear force or spin, the more it will thin and decrease in viscosity, as the rate at which one layer of the fluid passes over

another increases, causing the fluid to break down differently. *Id.* at 214:8-13 (Bowman); *id.* at 500:21-504:1 (Hanes).

For these reasons, the equipment, conditions, and parameters under which one tests a non-Newtonian thixotropic fluid are "critical" to determining viscosity. *See, e.g.*, *id.* at 201:1-16, 212:21-214:17 (Bowman) ("What happens is if you change viscometers with different spindles you get different viscosities, because this function of this product, specifically a BromSite product, the way it's formulated, if you change the rate at which the spindle is moving for this viscometer, as you go from high to low, the viscosity will decrease as the speed goes down."); *id.* at 442:9-12 (Olejnik) ("The heat history for sterilization, the mixing conditions, etc. [impact the final formulation's viscosity]."). In turn, where "equipment and conditions are specified [in a patent], it is imperative that the same equipment and conditions be used when attempting to reproduce viscosity data." *Id.* at 439:2-7 (Olejnik); *id.* at 538:4-8 (Hanes) ("[I]f you change anything, you could get different viscosity values."); *id.* at 216:18-20 (Bowman) ("[I]f you pick a viscometer, you have to pick a viscometer that basically will give you exactly the same results that one is using here.").

2. Methods for Measuring Viscosity Specified in the '999 Patent

The '999 Patent discloses two methods for measuring viscosity:

> The [polycarbophils] . . . give aqueous solutions or suspensions having viscosities ranging from about 1,000 to about 2,000 or 5,000 to about 20,000 cps respectively, as measured at room temperature (about 25° C.) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm . . . . Alternatively, the viscosity can be 1000 to 3400 cps as measured with a Brookfield cone and plate viscosity DV-II+ with the spindle No. CP-52 at 6 rpm.

JTX No. 001, at 12:19-32; Tr. at 540:5-7 (Hanes) ("Q. Dr. Hanes, we would agree that the '999 Patent discloses two possible methods for measuring viscosity, correct? A. Yes."). Plaintiffs argue that Defendants' ANDA infringes the '999 Patent's viscosity limitation when tested under Method

2.

Method 2 is not just a preferred embodiment, but an implicit or inherent part of the claimed viscosity limitation. *Infra*. This is so because of the nature of non-Newtonian thixotropic fluids, whose viscosity can vary widely depending on minute changes in the testing environment, as referenced above and explained more fully below. All experts and parties acknowledge this scientific fact. Without a known, precise measurement approach, a person of ordinary skill in the art ("POSA")[8] would not be able to replicate the invention with any degree of certainty about whether she is infringing the viscosity range in Claim 1. For example, if a chef fails to state in a complex recipe for a sauce how long to simmer/stir the ingredients, or whether to cover the pot, it would be difficult—even for another chef—to approximate the resulting dish. Method 2 in the '999 Patent provides a benchmark against which a POSA can make a reliable comparison in this sense. As Plaintiffs themselves elicited from Dr. Hanes on cross-examination, "if you change the conditions under which you measure [the] viscosity of a thixotropic fluid like BromSite, you may not be able to make a good comparison [between viscosity values]." Tr. at 538:20-539:18 (Hanes). A POSA therefore "would keep the [testing] conditions the same," or else "for what we are talking about here, to try to establish that one viscosity is exactly the same or within the right range, [ ] it would be very difficult." *Id.* at 539:15-18 (Hanes).

3. Methods for Measuring Viscosity Referenced in the NDA

Plaintiffs' NDA for BromSite, which they submitted to the FDA to obtain approval to market their drug publicly, references "analytical test results" for ISV-303, the 2006 clinical trial which led to the '999 Patent and the BromSite product, "where DuraSite was shown to be effective in increasing ocular residence time." *Id.* at 521:25-522:3 (Hanes) ("[The NDA] directs you to

8 I discuss *infra* what knowledge/experience a POSA would have based on the parties' (largely identical) representations.

analytical test results of ISV-303 clinical and registration stability batches."); *id.* at 426:10-12 (Olejnik) (stating that the phrase "[s]ee Scintiprox report" in BromSite's NDA refers to InSite's viscosity measurements for ISV-303). InSite tested the viscosity of ISV-303 using the following techniques:

- A known reference standard to ensure the accuracy of the measurement calibration. PTX No. 17-F, at 3940-41; Tr. at 427:19-428:1 (Olejnik).
- A 5X LV DV-II + CP viscometer. PTX No. 17-F, at 3968. "LV" refers to the spring type used in the instrument. Tr. at 432:24-433:1 (Olejnik). The maximum measurable viscosity for the "LV" spring is 1,550 cps. *Id.* at 446:20-21, 433:5-10 (Olejnik).
- Centrifuged samples at 1,000 rpm for 2 minutes to remove bubbles in the formulation. PTX No. 17-F, at 3962-63.
- Measure for viscosity after 3 minutes, when "the display reading [ ] stabilized." *Id.* at 3962, § 6.3; Tr. at 263:4-18 (Bowman).
- "The viscosity readings below 10% range is discredited and not used due to potential viscosity error according to Brookfield." PTX No. 17-F, at 3968; Tr. at 440:18-441:1 (Olejnik).

DTX No. 050. With respect to this ISV-303 product, InSite specifies a viscosity of "about 1500 cP" and a "range of 1000 cP – 2000 cP." PTX No. 017-B; Tr. at 399:14-18 (Olejnik) ("[T]he composition which they denoted as ISV-303, which is a BromSite composition, is a viscous solution formulation with a viscosity of about 1,500 cP . . . . The viscosity is maintained within the range of 1,000 cP to 2,000 cP."). The ISV-303 data includes batch measurements to this end. The batches measure 1410 cps, 1407 cps, 1236 cps, 1321 cps, 1349 cps, and 1325 cps, respectively, Tr. at 524:18-525:7 (Hanes), all within "about 1,000 to about 3,400 cps," which is the range in the '999 Patent, and "about 1,000 to about 2,000 cps," which is the range for ISV-303. *Id.* at 525:15-20 (Hanes).

ii. Conclusions of Law

1. Importance of Specified Testing Method

As an initial matter, when a patent specifies a testing method, particularly for a non-

Newtonian thixotropic fluid such as BromSite, which is highly susceptible to viscosity changes based on test conditions/parameters, the method in the patent is the only salient comparator for purposes of determining infringement, unless it is identifiable as part of a POSA's general background knowledge based on a convention in the field or standard industry practice. *See, e.g.*, *Marine Polymer Techs., Inc. v. HemCon, Inc.*, 659 F.3d 1084, 1094 (Fed. Cir. 2011) ("[C]laims specifically required an *elution test* score of zero, but did not reference any other testing method despite the fact that the specification disclosed four distinct testing methods . . . . Given the specification's reference to three other tests and the reference in the claims to only the elution test, we conclude that original claims 12 and 20 required a showing of no reactivity on only the elution test."), *reh'g en banc granted, opinion vacated*, 475 Fed. App'x. 315 (Fed. Cir. 2012), *on reh'g en banc*, 672 F.3d 1350 (Fed. Cir. 2012); *infra* (collecting cases on necessity of disclosing measurement method in context of indefiniteness).

When so specified, a testing method constitutes an implicit or inherent element of the claim term to which it refers and necessarily excludes other testing methods or measurement approaches from the scope of the relevant claim. *See, e.g.*, *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question."); *Cultor Corp. v. A.E. Staley Mfg. Co.*, 224 F.3d 1328, 1331 (Fed. Cir. 2000) ("[T]he Guzek patents do not define their polydextrose purification process in terms of any acid catalyst, but only in terms of a citric acid catalyst. By explicitly limiting the subject matter to that produced using a citric acid catalyst, the inventors limited their claimed invention."). As a result, any testing purporting to

show infringement on viscosity must have been conducted according to the methods specified in the '999 Patent.

2. Disputes about Measurement Approaches Fall Under Infringement

Numerous cases have held that issues relating to testing methods or measurement approaches are properly addressed, not only under a defendant's indefiniteness defense, but as part of a plaintiff's affirmative case for infringement. *See, e.g.*, *ADC Telecommunications, Inc. v. Switchcraft, Inc.*, 281 Fed. App'x. 989, 992 (Fed. Cir. 2008) (finding it relevant to infringement analysis that claim "does not mention, much less require, any particular testing method for the disputed limitations" and that "specification also lacks any clear indication that a particular testing method is required"); *Union Carbide Chemicals & Plastics Tech. Corp. v. Shell Oil Co.*, 425 F.3d 1366, 1377 (Fed. Cir. 2005) ("Because the claim does not require an exact match to the accused processes, Union Carbide had only an obligation to show that its test parameters sufficiently covered the range of conditions in each of the 69 accused commercial processes."), *overruled on other grounds by Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 576 F.3d 1348 (Fed. Cir. 2009); *Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1365 (Fed. Cir. 2014) ("[T]he dispute as to literal infringement turned on whether the patent required virtual dissection of hard agglomerates prior to particle size measurement."); *3M Innovative Props. Co. v. GDC, Inc.*, No. 13-1287, 2015 WL 2381046, at *4, *20 & n.12 (D. Minn. May 19, 2015) (observing same and collecting cases).

3. Defendants' ANDA

I turn next to the merits of the parties' infringement dispute, starting with Defendants' ANDA, which usually controls the inquiry. *Bayer*, 212 F.3d at 1246-50. Defendants' ANDA here specifies a viscosity between 200 and 400 cps, well below the range disclosed in the '999 Patent.

Tr. at 408:4-14 (Olejnik). On its face, this appears to be a non-infringing number. *See, e.g.*, *Ferring B.V. v. Watson Laboratories, Inc.-Fla.*, 764 F.3d 1382, 1388-89 (Fed. Cir. 2014) (finding no infringement under *Bayer* where ANDA specification required not less than 75% tranexamic acid to dissolve in 45 minutes, "because the patents-in-suit required that *less than* about 70 [%] by weight tranexamic acid be dissolved at 45 minutes") (emphasis in original); *Jeneric/Pentron, Inc. v. Dillon Co.*, 205 F.3d 1377, 1382-83 (Fed. Cir. 2000) (holding that "claim specifies 0-1% cerium oxide," while accused product "contains 1.61%—an amount well outside the precisely claimed range"); *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1320-22 (Fed. Cir. 2001) (holding that claim term requiring polymer density "below about 0.91 g/cm^3" not infringed by polymer with density of 0.912).

However, not only did Defendants fail to offer *independent*—rather than in-house—laboratory testing for their product's viscosity, Tr. at 415:20-23 (Olejnik); Dahibhate Depo. Tr. at 223:1-223:3 ("Q: Was all of this testing performed in-house at Lupin? A: Yes."), but their in-house testing involved both "different methods" and "different parameters" when "compared to the '999 Patent." Tr. at 404:15-16 (Olejnik). In particular, Defendants used "the Brookfield R/S Plus Rheometer [and] a spindle of C-71-1 using a speed of 15 revolutions per minute." *Id.* at 404:19-21 (Olejnik). That is, a different viscometer, spindle, and speed than "either of the methods" disclosed in the '999 Patent. *Id.* at 404:12-405:9 (Olejnik). Defendants' spindle was "three times bigger," which "create[d] different mechanical forces." Tr. at 21:2-4 (counsel). The spindle speed was also 2.5 times greater, which "generate[d] additional shearing forces" and "cause[d] the sample size to break down in a different way." *Id.* at 21:21-24 (counsel). Accordingly, Defendants' ANDA on its face is not dispositive of infringement on viscosity.

4. The EAG Report

Because the ANDA fails to follow the methods in the '999 Patent when measuring viscosity, neither party can rely on it for purposes of infringement. Still, Plaintiffs bear the burden of proving infringement on all claim limitations by a preponderance of the evidence. *See, e.g.*, *Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998) ("If even one limitation is missing or not met as claimed, there is no literal infringement."); *Purdue Pharma Prod. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 362 (D. Del. 2009), *dismissed*, 370 Fed. App'x. 80 (Fed. Cir. 2009), *aff'd*, 377 Fed. App'x. 978 (Fed. Cir. 2010) ("Plaintiffs bear the burden of proving that the accused product meets each and every limitation of the construed claims by a preponderance of the evidence."); *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997).

To carry their burden, Plaintiffs submitted a report from EAG Laboratories indicating that Defendants' generic has basically the same viscosity as BromSite. The report is the primary evidence—and the only independent evidence Plaintiffs have offered—on infringement. EAG measured the viscosity of both BromSite and the ANDA product multiple times. PTX No. 143; Tr. at 414:10-15 (Olejnik). EAG used a Brookfield RVDV cone and plate viscometer with a CP-52 cone to do so, at 25 degrees centigrade and 6 rpm, consistent with Method 2 in the '999 Patent. Tr. at 416:3-23 (Olejnik). Using these techniques, EAG reported BromSite's average viscosity to be 1,518.62 cps, plus or minus 46.08 cps. *Id.* at 418:7-17 (Olejnik). EAG also reported the ANDA product's average viscosity to be 1,179.62 cps, plus or minus 66.83 cps. *Id.* at 418:18-420:5 (Olejnik). Both averages are "about 1,500 cps" and "between 1,000 and 2,000 cps," as with the ISV-303 data, and between 1,000 and 3,400 cps, as disclosed in the '999 Patent—even when accounting for the standard deviation. *Id.* at 444:10-445:11 (Olejnik). Tables summarizing EAG's results are reproduced below, with relevant information highlighted.

Table 1. Brookfield Viscosity Results for Method Development (BromSite (bromfenac ophthalmic solution), 0.075%, 5mL Lot: V18E02 Exp: MAY 20) (S2)

Sample Number	Spindle	RPM	%Torque	Viscosity (cPs)	Average Viscosity (cPs)	Statistics
S2	CP52	6	9.0%	1488.30	1518.62	Standard Deviation = ±46.08
S2	CP52	6	8.8%	1455.23		
S2	CP52	6	9.5%	1570.98		
S2	CP52	6	9.2%	1521.37		Percent Relative Standard Deviation = 3.0%
S2	CP52	6	9.5%	1570.98		
S2	CP52	6	9.1%	1504.84		

Table 2. Brookfield Viscosity Results for Sample Evaluation (Bromfenac Ophthalmic Solution, 0.075%, 5mL Lot: H890057 Exp: 01/2020) (S1)

Sample Number	Spindle	RPM	%Torque	Viscosity (cPs)	Average Viscosity (cPs)	Statistics
S1	CP52	6	7.5%	1240.25	1179.62	Standard Deviation = ±66.83
S1	CP52	6	6.7%	1107.96		Percent Relative Standard Deviation = 5.7%
S1	CP52	6	7.2%	1190.64		

5. Defendants' Challenges to the EAG Report

When a plaintiff relies on independent testing to carry its burden, its test results of course must be reliable. *See, e.g.*, *Daubert v. Merrell Down Pharms.*, 509 U.S. 579 (1993). Courts have found generic products to be both infringing and non-infringing depending on whether the tests a plaintiff submits bear sufficient indicia of reliability. *Infra*. To this end, Defendants challenge five aspects of EAG's methodology: EAG did not (1) specify how much spin time passed before it took measurements, (2) report centrifugation, (3) use the proper spring in its viscometer, (4) ensure the spindle torque exceeded 10%, or (5) obtain results sufficiently similar to InSite's for ISV-303. *See, e.g.*, Tr. at 523:5-9, 497:10-516:24, 507:3-508:6, 509:11-516:19 (Hanes) (acknowledging that his "entire direct was focused on EAG"). When compared solely to the method used to test the ISV-303 data, Defendants conclude, the EAG report "imprecise" and "unreliable." Def. Br., at 11.

a. The ISV-303 Data Is the Wrong Comparator and Not Disclosed in the '999 Patent

As a preliminary matter, Defendants erroneously attack the EAG report by relying on comparisons with ISV-303. Def. Br., at 11 ("EAG *did not* follow the FDA-approved viscosity test method.") (emphasis in original). The '999 Patent contains just two methods for measuring

viscosity, neither of which discloses or incorporates, or references or contemplates, the methods underlying ISV-303. JTX No. 001, at 12:19-32. Measuring viscosity by a different standard or using different techniques would effectively eliminate an essential claim element. Because the two methods disclosed in the '999 Patent are the only methods by which Defendants can compare viscosities, Tr. at 538:20-539:18 (Hanes), I find unpersuasive Defendants' argument focusing on apparent discrepancies between the EAG report and ISV-303.

b. The EAG Report Did Not Report Time Before Measurement and Is Unreliable to that Extent

The parties do not substantively dispute that EAG applied Method 2 in the '999 Patent. *See, e.g.*, Tr. at 542:20-23 (Hanes) ("I would say I don't have evidence [suggesting otherwise]."); *id.* at 416:20-23 (Olejnik) ("Q. . . . And so, Dr. Olejnik, is the method that EAG used one of the methods that was disclosed in Column 12 of the '999 Patent? A. Yes, they did."); *id.* at 416:3-15 (Olejnik) (noting that, in EAG's "Method development" section, they stated that they looked to the information specified in the '999 Patent to test viscosity). Defendants nevertheless point out a critical flaw in Method 2, which renders the report an unreliable basis on which to rest a claim of infringement: it does not specify a spin time before taking a viscosity measurement.

EAG's test ran for a "minimum" of one minute before EAG recorded a measurement, but EAG otherwise did not note how long it spun the samples, because the '999 Patent does not disclose a spin time. *Id.* at 503:8-504:1, 507:3-23, 514:8-515:5 (Hanes). EAG "just specified that they would let [the test] go for one minute. To me, that means they are not keeping track of how much longer after one minute that they take measurements, so it would be highly unlikely that they always measured at the same time." *Id.* at 542:25-543:4 (Hanes). According to Dr. Hanes, this could have changed—and in all likelihood did change—the result. "[I]t's critical to specify how long you let that spindle rotate before making the measurement if you're measuring a non-

Newtonian fluid . . . . And the reason for that is, again, because this thixotropy or even in non-Newtonian fluids that aren't thixotropic, you can still have a decrease [in viscosity] with increase in shear rate, but thixotropic decreases with how long you let that thing spin. So you have you pick the right time and make all your measurements at the same time, if you have a thixotropic material." *Id.* at 507:9-20 (Hanes). Dr. Hanes goes on: "a [POSA] would know about a thixotropic material, the viscosity can change as you're spinning; and as time goes on, it can get lower and lower and lower. So they should have said the exact time and made clear that they measured all the samples from both [Defendants'] product and the reference listed drug [BromSite] at the same exact time." *Id.* at 514:8-20 (Hanes). When asked specifically "if you took a viscosity reading at three minutes, you could get a different reading than if you took it at, say, five minutes," Dr. Hanes responds: "Absolutely. And that's a major problem because . . . if they knew looking at the patent spec that they wanted to get a certain result for their client . . . they could – you know, you could choose different times to achieve a result." *Id.* at 514:20-515:5 (Hanes). By contrast, when testing ISV-303, InSite waited three minutes before taking a viscosity reading, so that its results could be reliably compared to each other and other products.

Dr. Hanes' testimony that differences in spin time can, in both theory and practice, produce different viscosities for non-Newtonian thixotropic fluids is not only credible but dispositive on infringement. His reasoning is firmly grounded in the science, and as important, Plaintiffs fail to offer any evidence to the contrary—for example, that viscosity does not materially change as long as a lab waits at least one minute, as EAG did, or that a POSA would know based on her background knowledge exactly when to take a measurement. *Compare Astra Aktiebolag v. Andrx Pharms., Inc.*, 222 F. Supp. 2d 423, 490 (S.D.N.Y. 2002) ("Obtaining pH measurements using an electrode and a pH meter, as Dr. Davies did, however, is a standard, reliable method for

determining whether a material has alkaline characteristics. Every witness who testified on this subject, and the manufacturers of the substances like HPMC that were tested, acknowledged that pH-electrode testing is a standard analytical tool.") (internal citation omitted), *aff'd sub nom.*, *In re Omeprazole Pat. Litig.*, 84 Fed. App'x. 76 (Fed. Cir. 2003), *with Zenith Lab'ys*, 19 F.3d at 1423 ("[H]ere major problem arises. In order to establish its case, Bristol had to show that the accused compound infringed the claim contained in the patent. This required Bristol to show that the diffraction pattern of cefadroxil DC following its conversion *in vivo* displayed the same diffraction pattern as that of the claimed compound. The district court, instead of requiring the comparison of the accused compound following conversion to be made with the lines specified in the claim, allowed Bristol to make the comparison with the diffraction pattern exhibited by a sample (the reference pattern) of a material considered by Bristol to be the patented compound.").

When evaluating infringement evidence akin to the EAG report, courts have found reliability to be critical, and have both affirmed and invalidated patents on that basis. *Compare Precision Fabrics Grp., Inc. v. Tietex Int'l, Ltd.*, 367 F. Supp. 3d 487, 499, 514 (D.S.C. 2019) (upholding jury's verdict of non-infringement on motion for judgment as a matter of law because plaintiff's tests were "not reliable because of the testing conditions," plaintiff "bore the burden of proof on the question of literal infringement," and as such, the jury "was free to disbelieve" the evidence/expert testimony), *aff'd*, 790 Fed. App'x. 208 (Fed. Cir. 2020); *Eli Lilly & Co. v. Perrigo Co.*, 202 F. Supp. 3d 918, 1016 (S.D. Ind. 2016) ("Without knowing the exact amount of liquid used by Dr. Slocum, in his wet test, it is impossible to know the effect of such imprecision on his observations and findings. Accordingly, Dr. Slocum's failure to ensure that he was applying the amount of liquid indicated in Actavis's and Perrigo's labeling completely undermines the reliability of his opinion that the Actavis and Perrigo applicators infringe the '944 patent's 'wall'

limitation when used in accordance with those labeling instructions."), *aff'd*, 718 Fed. App'x. 953 (Fed. Cir. 2017), *with Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1289 (Fed. Cir. 2010) (vacating summary judgment on non-infringement because factfinder could reasonably conclude that the accused product would infringe, based on plaintiff's direct pharmacokinetic data and evidence that commercial embodiment and accused product were bioequivalent); *ClearValue v. Pearl River Polymers, Inc.*, 242 F.R.D. 362, 377 (E.D. Tex. 2007) (crediting "an expert report prepared to discuss an independent test of the accused products' molecular weight"), *aff'd in part, rev'd in part and remanded sub nom.*, 560 F.3d 1291 (Fed. Cir. 2009). The EAG report in this case is unreliable to the extent that its spin time parameter is vague and imprecise.

Plaintiffs argue that Defendants cannot demonstrate that EAG *actually measured* viscosity at different times. Defendants, and the Court, can only speculate that EAG waited for more than one minute, or more than three minutes, or however long, to take its measurements—either for different samples of the same product or for one product versus the other. *Id.* at 543:5-6 (Hanes) ("They didn't – they didn't record the time and that was the problem."); *id.* at 544:21-22 (Hanes) ("[T]hey could have done it at different times . . . . That's possible. I don't want to believe that somebody would do that, but, you know, they are the client."); *id.* at 545:3-7 (Hanes) ("Q: So your answer, Dr. Hanes, is though while these are possibilities, you don't have anything that tells you one way or the other that that's what was done, correct? A: I think that's fair."). Fatal to Plaintiffs' rebuttal is that it is not Defendants' burden to submit such evidence. Rather, it is Plaintiffs' burden to show why, as a scientific principle, spin time is not relevant or dispositive when testing non-Newtonian thixotropic fluids, or that EAG in fact measured viscosity at the same time each time, or how a POSA would otherwise know how long to wait to test the sample such that failure to

expressly state a spin time is not a problem. The EAG report is unhelpful to the extent that these are simply absent. Put differently, a POSA would not know when to take a reading to measure viscosity, which, based on Dr. Hanes' unrefuted testimony, could cause the reading to materially change, depending on how long the POSA decides to wait.

Perhaps recognizing this issue with the EAG report, Plaintiffs submit other evidence to demonstrate that Defendants "more likely than not" infringed on viscosity. *Vanda Pharms.*, 887 F.3d at 1125. None, however, is availing. First, Plaintiffs point to two defense witnesses who testified that their generic's viscosity is the "same" as BromSite's. *See, e.g.*, Dahibhate Depo. Tr. at 99:14-100:1, 101:24-102:21; Avachat Depo. Tr. at 146:18-24 ("Q: Does Lupin expect the viscosity of its proposed generic to be the same or similar to the viscosity of BromSite? A: In fact, the product has been designed in that manner, so it has to have not just viscosity, all parameters which are similar to the reference listed drug."). But Plaintiffs cannot carry their burden by comparing commercial products to each other. *Zenith Lab'ys*, 19 F.3d at 1423 ("It is error for a court to compare in its infringement analysis the accused product or process with the patentee's commercial embodiment or other version of the product or process; the only proper comparison is with the claims of the patent.").

Second, according to Defendants' own in-house testing, its ANDA product and BromSite exhibit similar viscosities. Defendants measured BromSite's viscosity as between 308.5045 cps and 331.985 cps, and its generic's viscosity as between 307.4356 cps and 325.2328 cps. Tr. at 415:5-19 (Olejnik); *id.* at 408:4-18 (Olejnik) ("They are the same, and they fall within the same range . . . . They are in the order of magnitude of 300 cps."); *id.* at 525:24-526:14 (Hanes) ("To my recollection, they were similar."). Even so, the problem is that Defendants did not conduct their tests by following Method 2 in the '999 Patent, which is fatal because proof of infringement

must be based on patent terms/claims alone, including any measurement approaches so disclosed. *Supra.*

Third, Plaintiffs assert, it is "logically and legally problematic" that Defendants could concede that their product is "pharmaceutically, chemically, qualitatively, and quantitively the same as BromSite while simultaneously exhibiting exactly one distinction in its physical and chemical properties—and that one distinction happ[ens] to be a viscosity parameter that is recited in the asserted '999 Patent." Such an argument cannot suffice as a matter of law. Essentially, Plaintiffs' claim is that they need not adduce evidence of infringement on one limitation as long as they have adduced evidence of infringement on the other limitations, a position which runs counter to well-established law. *See, e.g.*, *Zenith Lab'ys*, 19 F.3d at 1423. Even assuming that Plaintiffs could carry their burden in this manner, it is plausible that viscosity might differ where other product characteristics do not, because viscosity depends on factors beyond ingredients. *See, e.g.*, Tr. at 529:17-20 (Hanes) ("I think that their goal was to make a product that's bioequivalent. So that would have a viscosity that's, you know, could be different but still have something that's bioequivalent."). Accordingly, Plaintiffs have not satisfied their burden of proving literal infringement.

III. INVALDITY – INDEFINITENESS

I turn next to invalidity defenses.[9] An issued patent is presumed to be valid. 35 U.S.C. § 282. That presumption may be overcome by clear and convincing evidence to the contrary.

9 Prior to the Supreme Court's decision in *Cardinal Chem. v. Morton Int'l, Inc.*, 508 U.S. 83 (1993), the Federal Court emphasized that "it was unnecessary to decide invalidity in cases where there was no infringement." *Brunswick Corp. v. United States*, 34 Fed. Cl. 532, 556 (1995). *Cardinal* reversed this trend, holding that a patent case does not become moot (in the sense of Article III) simply because a court finds non-infringement. 508 U.S. at 98-99. There, the Court ruled on a "necessary resolution of a counterclaim for a declaratory judgment," and emphasized the public's interest in finality. *Id.* at 101-02. In light of *Cardinal*, I find that it is appropriate to decide Defendants' invalidity claims to put an end to "endless litigation (or at least uncertainty) over the validity" of the '999 Patent. *Id.* at 102; *Blonder-Tongue Labs.,*

Microsoft Corp. v. i4i Ltd. P'ship, 564 U.S. 91, 95 (2011). Clear and convincing evidence is a "high bar," *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 644 (2015), requiring evidence which "places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are highly probable,'" *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 310 (1984)), and which can "'instantly tilt[] the evidentiary scales' in favor of its proponent when weighed against the opposing evidence." *ICI Uniqema, Inc. v. Kobo Prods., Inc.*, No. 06-2943, 2015 WL 668282, at *8 (D.N.J. Feb. 17, 2015) (quoting *Colorado*, 467 U.S. at 310). Defendants raise indefiniteness, obviousness, and inequitable conduct defenses. I address each in turn.

A. Indefiniteness

Under 35 US.C. § 112, a patent may not issue if its claims are indefinite. *Id.* (providing that a patent "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same"). To be definite, a patent's claims must "inform those skilled in the art about the scope of the invention with reasonable certainty," *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910-11 (2014), when read in light of the specification and prosecution history. *United States v. Adams*, 383 U.S. 39, 48-49 (1966) (specification); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 741 (2002) (prosecution history). Definiteness is measured from the

Inc. v. University of Ill. Found., 402 U.S. 313, 338 (1971). This is particularly so because Defendants' indefiniteness defense arises from the same factual issue as literal infringement (spin time) and sheds additional light on why Plaintiffs fail to carry their burden on viscosity. The public interest in a final decision on the patent-in-issue plus the nexus between literal infringement and indefiniteness form a "compelling reason[]" to address Defendants' invalidity defenses despite finding their generic not to infringe. *Brunswick*, 34 Fed. Cl. at 558.

perspective of a POSA at the time the patent is filed. *General Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 371 (1938); *Nautilus*, 572 U.S. at 908.

"Reasonable certainty" does not require "absolute or mathematical precision." *Biosig Instruments, Inc. v. Nautilus*, *Inc.*, 783 F.3d 1374, 1381 (Fed. Cir. 2015) (quotations and citation omitted); *Augme Techs. v. Yahoo!, Inc.*, 755 F.3d 1326, 1340 (Fed. Cir. 2014) (holding that a limitation "clear on its face" "unquestionably meets [the *Nautilus*] standard"). As such, the Federal Circuit has "refused to require that a patent disclose details as to every possible variable that may affect the calculation of a measured value or range of values recited in a patent claim." *Pac. Coast Bldg. Prod., Inc. v. CertainTeed Gypsum, Inc.*, 816 Fed. App'x. 454, 459 (Fed. Cir. 2020). Although "[s]ome modicum of uncertainty" is permissible in this regard, *Nautilus*, 572 U.S. at 899, a patent must still "disclose a single known approach or establish that, where multiple known approaches exist, a [POSA] would know which approach to select." *Dow Chem. Co. v. Nova Chemicals Corp. (Canada)*, 803 F.3d 620, 630-31 (Fed. Cir. 2015); *Teva Pharm. USA, Inc. v. Sandoz Inc.*, 789 F.3d 1335, 1344-45 (Fed. Cir. 2015) (holding claim indefinite where molecular weight could be measured three different ways and would yield different results with each way, and patent and prosecution history did not provide guidance as to which measure to use). "Particularly this is so where different approaches to measurement are involved." *Dow*, 803 F.3d at 631; *Teva*, 789 F.3d at 1341, 1344-45. If a measurement method is not a POSA's "default" or there is not "convergence in the field" on it, and "the intrinsic and extrinsic evidence does not narrow the field to the one aspect meant to establish the boundary of the invention," that is "the hallmark of an indefinite term."[10] *Otsuka Pharm. Co. v. Torrent Pharms. Ltd. Inc.*, 151 F. Supp.

10 The Federal Circuit has made it clear that a patent is not indefinite merely because it fails to specify which method of measurement should be used. *Takeda Pharm. Co. Ltd. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1366-67 (Fed. Cir. 2014); *Purdue Pharm. Prods., L.P. v. Actavis Elizabeth, LLC*, Nos. 12-5311, 13-5003, 2014 WL 2624787, at *5 (D.N.J. June 11, 2014). Yet, in such circumstances, there are usually

3d 525, 548-49 (D.N.J. 2015), *aff'd sub. nom.*, 694 Fed. App'x. 808 (Fed. Cir. 2017); *Enzo Biochem Inc. v. Applera Corp.*, 780 F.3d 1149, 1153 (Fed. Cir. 2015) (observing that "relevant science" constitutes extrinsic evidence).

As discussed in the context of the EAG report, Method 2 in the '999 Patent does not specify a minimum or maximum spin time before taking a viscosity reading. Tr. at 507:3-20 (Hanes); *id.* at 398:1-12 (Olejnik) (confirming that patent mentions two testing methods only). The patent is silent on this parameter even though all experts agree that viscosity cannot reliably be measured or compared without comprehensive, precise information on the testing environment. *See, e.g.*, *id.* at 216:12-20 (Bowman) (testifying generally that, to get the same measurements, a POSA must use the same instruments under the same conditions). Dr. Hanes calls this gap in Method 2 a "major problem." *Id.* at 514:20-515:5 (Hanes). Since viscosity changes over time and with force for fluids like BromSite, it is essential to identify at what time a POSA should measure it. *Id.* at 507:6-20 (Hanes); *id.* at 514:8-515:5 (Hanes).

Also, as discussed *supra*, Plaintiffs did not adduce evidence that spin time is irrelevant from a scientific perspective, or that a POSA would know by default or based on some industry standard what time point to select. *See, e.g.*, *CertainTeed*, 816 Fed. App'x. at 460 ("Pacific Coast has not pointed to any extrinsic evidence that supports its claim that a skilled artisan would either

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several possible accepted methods to measure whether a claim limitation is met, and the choice of method does not fundamentally alter the test result. *W.L. Gore & Assocs., Inc. v. C.R. Bard, Inc.*, No. 11-515, 2015 WL 12843216, at *10 n.16 (D. Del. July 15, 2015), *report and recommendation adopted in part, rejected in part*, 2015 WL 12831300 (D. Del. Sept. 28, 2015); *Kaneka Corp. v. Zhejiang Med. Co.*, No. 11-02389, 2018 WL 2718036, at *13 (C.D. Cal. Apr. 5, 2018) (rejecting indefiniteness argument at summary judgment when, although "Defendants have presented evidence obtained during the ITC Proceedings showing that refrigerating or freezing samples for different durations can lead to different mole % measurements and ratios," it is "far from clear whether these differences are 'outcome-determinative' . . . as determined by a person of ordinary skill in the art"), *aff'd sub nom.*, 767 Fed. App'x. 998 (Fed. Cir. 2019). Here, on the other hand, the '999 Patent fails to specify a measurement method, which is critical given the nature/characteristics of the patented solution, *and* the method matters to the outcome in a non-trivial way. *Infra*.

know which of the ASTM's configurations to choose or to average the tests together. Nor does Pacific Coast identify any evidence, apart from Mr. Risinger's conclusory testimony, that the scoring depth does not matter."); *Otsuka*, 151 F. Supp. 3d at 548 ("In this case, the wording of the claim term 'mean' and specification may be construed as designating an instrument by which to conduct a measurement of 'mean particle size,' but nothing therein guides the skilled practitioner whether to utilize the 'volume weighted mean' or the 'surface weighted mean' that such a device reports as measurements. The choice of 'volume' or 'surface' matters because each type lends to a different result. Looking then to extrinsic evidence, Otsuka has not demonstrated that 'volume weighted mean' is the default measurement that the ordinary skilled practitioner would select."). To the contrary, as Dr. Hanes states, a POSA would "know about" the importance of plainly specifying a spin time from the beginning to ensure that one can "measur[e] all samples . . . at the same exact time." Tr. at 514:13-20 (Hanes).

The data both parties emphasized at trial demonstrates the lack of a general scientific consensus on spin time and the impact disparate spin times can have on viscosity. Starting with the ISV-303 tests, where InSite measured viscosity for its precursor to BromSite after three minutes, "at which point the display reading has stabilized," PTX No. 17-F, at 3961-62, the batch results were 1410 cps, 1407 cps, 1236 cps, 1321 cps, 1349 cps, and 1325 cps, respectively. Tr. at 524:18-525:7 (Hanes). Comparing those data points with the EAG tests, where EAG measured viscosity for BromSite at some unspecified time "after 1 minute," the batch results there ranged from 1488 to 1570 cps, a difference of several hundred cps on what Plaintiffs say is essentially the same product. PTX No. 143, at 2. This does much to indicate that there is no "convergence upon [a] convention in the field" as to how long to wait before taking a measurement, *Otsuka*, 151 F. Supp. 3d at 548-49, and that even a small fluctuation in spin time can be outcome-determinative.

Accord Honeywell Int'l, Inc. v. ITC, 341 F.3d 1332, 1336, 1339 (Fed. Cir. 2003) (noting that "neither the claims, the written description [of the patent at issue], nor the prosecution history references any of the four sample preparation methods that can be used to measure the MPE," and that depending upon which method was used, "the calculated MPE for a given sample can vary greatly"). While the ISV-303 data is the wrong comparator for purposes of determining literal infringement, with respect to indefiniteness, it is nonetheless illustrative.

Of course, the viscosity measurements for Defendants' generic in the EAG report all fall within "about 1,000 to about 3,400 cps," Tr. at 525:15-20 (Hanes), or the claimed range in the '999 Patent, which on the surface supports infringement. But the inherent flaw is that there is no given reason, nor any reason appearing in the patent, why EAG chose to wait "at least 1 minute," rather than some other length of time. The '999 Patent does not specify any waiting period despite the fundamental importance of identical testing conditions. To ignore or downplay that omission would run contrary to the very purpose of disclosing a measurement approach. Given that the spin time parameter is missing, I cannot conclude that the '999 Patent is definite as to the method for testing viscosity, even if Claim 1 discloses a particular viscosity range. *Dow*, 803 F.3d at 633-35 (holding that, because four known test methods produced different results, "the method chosen for calculating the slope of strain hardening could affect whether or not a given product infringes," and thus invalidating the claims as indefinite); *CertainTeed*, 816 Fed. App'x. at 459 ("We agree with the district court that the '568 patent fails to provide guidance to a skilled artisan for how to measure the newly coined characteristic 'scored flexural strength' with reasonable certainty. While the claims recite a particular value for 'scored flexural strength,' i.e., 'about 22 pounds per 1/2 inch thickness,' the claims and specification fail to explain what the value represents or how to consistently and reproducibly measure this new characteristic."); *Teva*, 789 F.3d at 1338, 1341

(finding claim term indefinite even though patentee's expert testified that a POSA could otherwise determine which method was most appropriate).

Rather, the '999 Patent leaves a POSA who attempts to match its viscosity range to establish infringement, or to distinguish a product as non-infringing, "to consult the unpredictable vagaries of any one person's opinion" without "objective boundaries" on spin time. *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371, 1374 (Fed. Cir. 2014). It also leaves a POSA without an "informed and confident choice" among "contending" spin times. *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 698 (Fed. Cir. 2019); *Media Rights Techs., Inc. v. Capital One Fin. Corp.*, 800 F.3d 1366, 1371 (Fed. Cir. 2015). That does not suffice as "reasonable certainty" under *Nautilus*.

Koninklijke Philips N.V. v. Zoll Med. Corp., 656 Fed. App'x. 504 (Fed. Cir. 2016), provides an instructive contrast. In *Zoll*, the Federal Circuit upheld a jury verdict that a claim was definite even though the patent's specification did not provide details about some parameters for the testing conditions/equipment, such as the temperature of the procedure and age of electrodes. *Id.* at 526. Although the missing parameters introduced a degree of imprecision into the measurement of an attribute recited in the claims, according to the court, the jury could have reasonably "viewed the evidence on" the missing parameters as sufficient to create only a minor, inconsequential source of imprecision. *Id.* There was also expert testimony supporting the view that a POSA would have understood how to handle the missing parameters when reading the claim. *Id.* Here, on the other hand, the potential imprecision associated with not specifying a spin time is a "major problem," and Plaintiffs do not present any evidence to suggest that a POSA would know how long to spin a sample despite the '999 Patent's silence on that issue. Furthermore, Dr. Hanes' unrebutted

testimony was that a POSA would need to know spin time beforehand. *See, e.g.*, Tr. at 514:13-20 (Hanes).

Neither is this case like *Biosig Instruments*, 783 F.3d at 1377. In *Biosig*, the Federal Circuit held that a patent's prosecution history and claim language, coupled with a POSA's general knowledge, demonstrated that "a skilled artisan would understand the inherent parameters of the invention as provided in the intrinsic evidence" and that the claim term at issue "informs a skilled artisan with reasonable certainty of the scope of the claim." *Id.* at 1382–84 (concluding that a POSA would know that the term "spaced relationship" could not be "infinitesimally small nor greater than the width of a user's hands"). Plaintiffs do not point to any such evidence in this case. Because the '999 Patent does not specify a minimum or maximum spin time, or even a range, leaving a POSA to guess how long to wait before taking a measurement, I find by clear and convincing evidence that the claim term "viscosity" is indefinite. Such finding invalidates the '999 Patent, even if Defendants' generic were deemed to literally infringe.[11] *Honeywell*, 341 F.3d at 1340 (holding that claims containing the disputed term "melting point elevation" were "insolubly ambiguous, and hence indefinite" because "the claims, the written description, and the prosecution history fail [ed] to give . . . any guidance as to what [a POSA] would interpret the claim to require").

IV. INVALIDITY – OBVIOUSNESS

Under 35 U.S.C. § 103, a patent may not issue if its claims are obvious to a POSA in light of prior art.[12] *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1380 (Fed. Cir. 2009).

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11 Defendants also argue that the claimed viscosity *ranges* are indefinite. "In light of [my] disposition [I] need not reach this issue." *Dow*, 803 F.3d at 633 n.8.

12 Congress amended § 103 in 2013 as part of the Leahy-Smith America Invents Act ("AIA"). Here, however, both the date of the '999 Patent and the earliest effective filing date is March 5, 2009, so the pre-AIA version applies. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1341 n.4 (Fed. Cir. 2016). Under that version of the statute, "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious

Obviousness "is a question of law based on underlying findings of fact." *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). It turns on four inquiries: "(1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need." *Procter*, 566 F.3d at 994; *In re Cyclobenzaprine*, 676 F.3d at 1068; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966).

Because issued patents carry a presumption of validity, 35 U.S.C. § 282, a party seeking to invalidate a patent must demonstrate "by clear and convincing evidence that a [POSA] would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the [POSA] would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). Although any teaching, suggestion, or motivation to combine is useful, the analysis must be expansive and flexible rather than rigid. *KSR*, 550 U.S. at 415, 419; *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1328 (Fed. Cir. 2009) ("Common sense has long been recognized to inform the analysis of obviousness if explained with sufficient reasoning."). Finally, "while the presentation at trial of a reference that was not before the examiner does not change the presumption of validity, the alleged infringer's burden may be more easily carried because of this additional reference." *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000); *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1569 (Fed. Cir. 1996) (same); *cf. Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008) (holding that, where "the examiner considered the asserted prior art and basis for the validity challenge during patent prosecution, that burden [to prove obviousness] becomes particularly

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at the time the invention was made to a person having ordinary skill in the art ["POSA"] to which said subject matter pertains." 35 U.S.C. § 103(a).

heavy"). There is no dispute that the Examiner did not review Bowman I in prosecuting the '999 Patent.

A. Conclusions of Fact

i. Definition of POSA

I begin with how the parties define the POSA. As a rule, the definition of a POSA must encompass the inventor's educational level, type of problems encountered in the art, prior art solutions to those problems, rapidity of innovations, sophistication of the technology, and educational level of active workers in the field. *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citation omitted). The parties' POSA definitions here are essentially the same. *See, e.g.*, Tr. 999:12-1000:6 (Hanes); *id.* at 782:18-783:12 (Olejnik). The inventors of the '999 Patent each had a PhD. *Id.* at 124:25-125:9, 134:20-24, 135:7-11, 135:16-18 (Bowman). Various problems and their solutions—such as blink reflex, eye drainage systems, corneal barrier, need for high concentration and residence time, need for controlled release, need for viscosity enhancers, and need to limit inflammation/pain—were known. *Id.* at 556:22-562:10, 564:14-565:8, 620:19-621:25 (Hanes). And the POSA would be part of an ophthalmic development team, either with years of experience designing formulations or with equivalent experience conducting clinical trials. *Id.* at 999:12-1000:6 (Hanes); *id.* at 782:18-783:12 (Olejnik). The only dispute is education level. According to Dr. Hanes, workers in the field would have an advanced degree, *id.* at 496:21-24 (Hanes), whereas Dr. Olejnik suggests a bachelor's degree only. *Id.* 782:21-24 (Olejnik). Although both experts testify that any definitional difference does not change their bottom-line opinion "at all," *id.* at 999:12-1000:6 (Hanes); *id.* at 782:18-783:17 (Olejnik), in the Court's view, the POSA would have at least a bachelor's degree with an appropriately greater amount of work experience in the requisite field. Finally, the parties do not specify the POSA's

exact discipline. *Cf. Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC*, No. 14-7869, 2018 WL 9364037, at *6 (D.N.J. Apr. 25, 2018) (specifying medicinal chemistry, organic chemistry, or a closely related field). But here that is acceptable because of the manner in which the parties define the POSA: she could have different degrees. Presumably that is why the experts focused their definitions on training/experience. By way of example, Dr. Hanes has a PhD in chemical engineering with a post-doctoral fellowship in oncology, immunology, and neurosurgery, Tr. at 478:24-479:4 (Hanes), while Dr. Olejnik is a "pharmacist by [ ] first degree" with a PhD in "ion association drug transport" and years of work "in industry" in between. *Id.* at 369:20-370:7 (Olejnik); *accord Purdue*, 642 F. Supp. 2d at 368 ("A person of ordinary skill in the art at the time of the invention was one with experience as a formulator, a pharmacokineticist, and a clinician.").

ii. POSA's General/Background Knowledge as of March 5, 2009

As of March 5, 2009, the date of the '999 Patent, a POSA working in ophthalmic drug development would have known that topical ophthalmic solutions are commonly used for patients undergoing cataract surgery, *id.* at 553:20-556:21 (Hanes), and also about FDA-approved drugs for topical administration, *id.* at 621:14-627:1, 643:7-644:7 (Hanes), in particular NSAIDs. *Id.* at 555:5-9 (Hanes). By that date, the FDA had approved five: flurbiprofen (like ibuprofen), diclofenac, ketorolac, nepafenac, and bromfenac. *Id.* at 622:9-15 (Hanes). Bromfenac was a well-regarded, FDA-approved drug marketed as a topical ophthalmic NSAID under the trade name Xibrom. *Id.* at 860:8-11 (Olejnik); *id.* at 156:8-16 (Bowman).

A POSA would have further known about polycarbophils—specifically, that they were "industry standard," commercially available, bioadhesive, mucoadhesive, water insoluble, water swellable polymers used to increase bioavailability and residence time in the eye, including for drugs like progesterone, azithromycin, flurbiprofen, fluorometholone, and demulcents. *See, e.g.*,

id. at 570:6-589:14, 598:599:21 (Hanes); *id.* at 880:7-881:25 (Olejnik). Additionally, a POSA would "understand the standard types of excipients, ingredients, that you would include an ophthalmic preparation" to practice an invention, for example "water and buffering-adjusting agents," *id.* at 836:15-18, 837:17-18, 838:3 (Olejnik), "antioxidants, tonicity adjusters, viscosity-enhancing agents, thickeners, modifiers, and the like," *id.* at 838:25-839:2 (Olejnik), and how to use them "to adjust the osmolality." *Id.* at 838:12-16 (Olejnik).

Next, a POSA would have known about DuraSite, the drug delivery system InSite used for years to develop ophthalmic compositions with commercially available products:

- "DuraSite is composed of a cross-linked polyacrylic acid polymer, water and salts" and "a range of viscosities . . . . Upon the addition of water, DuraSite swells to ~100x its original weight." DTX No. 454_7; DTX No. 455_8.
- The DuraSite system "is bioadhesive, sustained release, and compatible with both water soluble and water insoluble molecules." DTX No. 454_8.
- "The ingredients in DuraSite sustained release technology are classified by the FDA as Category 1 GRAS (generally recognized as safe)," which "helps to facilitate worldwide approvals of drugs that contain it." *Id.*
- DuraSite was "designed to extend the residence time of a drug relative to conventional topical therapies," it "can be customized for delivering a wide variety of potential drug candidate," and "allows lower concentrations of a drug to be administered over a longer period of time." DTX No. 454_7; DTX No. 455_7; DTX No. 929_5; PTX No. 259, at 3 (discussing polycarbophils).
- "The combination of DuraSite and proven drug products" yields products with "increased efficacy and improved compliance through a reduced dosing frequency." *Id.*
- "Polycarbophil (Noveon AA-1)" was "extensively described for its bioadhesiveness and potential usefulness as a support matrix for sustained drug release." DTX No. 7_2 (citing articles published in 1997 and 2002).
- DuraSite used polycarbophils as the "sustained release topical ophthalmic delivery system that releases the drug at a controlled rate." DTX No. 3, at 5:1-4; DTX No. 25, at 12:50-51; DTX No. 142, at 13:53-58.

Finally, a POSA would have known that numerous factors affect the penetration-enhancing properties of ophthalmic formulations, as well as their residence time. This includes the presence and concentration of a polycarbophil such as DuraSite; the "log partition coefficient value" of an active ingredient, which, if greater than 2.0, "permits greater penetration," *id.* at 300:11-15

(Bowman); the presence of a sugar, which, when added to "a water-soluble medicament," can create "an improved release profile," *id.* at 670:16-18 (Hanes); the pH of the formulation, which affects how long it adheres to preocular tissue; "preservative[s]" like benzalkonium chloride; "chelators" like EDTA or citric acid; and "solubilizers" such as Poloxamer 407. *Id.* at 566:8-15, 681:8-9 (Hanes); *id.* at 334:11-14 (Bowman) ("Q. . . . And, Dr. Bowman, when it comes to these polycarbophil formulations, you agree that other excipients can affect performance, right? A. Other excipients can, yes."); *id.* at 839:14-20 (Olejnik) (testifying that a formulation can depend on "interesting interactions between excipients . . . the overall composition [of the formulation] . . . the drug molecule . . . [and other] physico-chemical characteristics").

iii. Prior Art References as of March 5, 2009

Defendants argue that the '999 Patent is obvious given various prior art references. Their expert, Dr. Hanes, bases his opinion on four combinations: Bowman I, Bowman I + Xibrom PI, Bowman I + Xibrom PI + Chandrasekaran, and Xibrom PI + Patel, with the caveat that other publications inform a POSA's background knowledge.[13] *Id.* at 697:10-11, 701:9-10 (Hanes). Patel refers to U.S. Patent No. 5,340,572, issued on August 23, 1994. DTX No. 253. It discloses sustained release of antibiotics with multiple amine groups. Tr. at 810:22-811:6 (Olejnik); *id.* at 591:5-7, 734:18-20 (Hanes); DTX No. 253, at 10:11-24. Chandrasekaran refers to U.S. Patent No. 5,188,826, issued on February 23, 1993. DTX No. 251. It discloses using a demulcent, such as polycarbophil, to treat dry eye. Tr. at 807:22-808:14 (Olejnik). It is also an over-the-counter medication. *Id.* at 741:24-742:1 (Hanes) (stating that he is not aware of any over-the-counter medications containing bromfenac). Xibrom PI, which is neither a patent nor a paper, but a set of

13 These publications include, *inter alia*, the Robinson and Hui paper, Robinson patent, Davis patent, Babcock patent, Bowman '231 patent, Roy patent, Asane article, Gua article, Chandran article, and Bowman 2009 article. *See, e.g.*, Tr. at 878:1-885:1 (Olejnik).

prescribing instructions, discloses using bromfenac to treat inflammation relating to cataract surgery. DTX No. 027_001; Tr. at 807:3-5 (Olejnik); *id.* at 648:15-649:2 (Hanes). It is "much less viscous" than BromSite and does not contain polycarbophil but rather povidone, another type of polymer. *Id.* at 745:19-20 (Hanes). Because I find that the '999 Patent is obvious in light of Bowman I alone, I do not opine on Defendants' other obviousness combinations.

iv. Bowman I Background

Bowman I is the primary prior art at issue here. Its "object" is to provide an ophthalmic composition that has "a low viscosity and is easily administered in liquid drop form to the eye," has "a pH of greater than about 6.7," and is a polycarbophil formulation. DTX No. 003, at 2:1-8, 1:5-41; Tr. at 257:19-25, 305:1-307:2 (Bowman). More generally, Bowman I is directed to "sustained release ophthalmic compositions that contain water soluble medicaments." *Id.* at 1:7-10; *id.* at 637:11-13 (Hanes) ("[T]he title of this patent is 'Sustained Release Ophthalmic Compositions.'"). Bowman I defines a "medicament" as "any substance or drug that is useful in treating or ameliorating a disease or medical condition." DTX No. 003, at 3:3-8. Although timolol, a beta blocker for glaucoma, is its preferred embodiment, *id.* at 3:31-33, Bowman I discloses a broader range of drugs, including other "beta blockers" such as "levobunolol, betaxolol and atenolol; antibiotics such as tobramycin, anti-inflammatory agents such as ibuprofen; antivirals; and anesthetics." *Id.* at 3:13-17. Bowman I does not mention bromfenac. Tr. at 707:2-5 (Hanes) ("Right, the word 'bromfenac' in black and white is not in Bowman I."); *id.* at 737:5-13 (Olejnik). Yet, as to what water soluble medicaments a POSA could practice in the invention, Claim 9 broadly discloses any one that is "lipophilic and has a log partition coefficient of at least 2.0, preferably 3.0 (using n-octanol/pH 7.4 buffer). In this way, the higher pH of the present invention will allow for better corneal penetration of the medicament." DTX No. 003, at 3:53-58.

Bowman I also discloses a sugar, sorbitol. When added to a low-viscosity formulation such as one containing timolol, it can control release over time. *Id.* at 3:38-52, 9:59-66, Fig. 1; Tr. at 804:5-23 (Olejnik) ("[W]ith the sugar, with the sorbitol, the formulation has been modulated to the extent where it's lowered the release rate significantly so, with a longer duration of action, as represented by the area under the curve."); *id.* at 719:9-20 (Hanes). "None of the prior art [before Bowman I] teaches the use of a sugar as a medicament release profile enhancer." DTX No. 003, at 2:46-47. "This result is surprising in that the prior art uses of sugars have been, in general, as nonionic osmolality enhancing agents." *Id.* at 2:40-43.

Bowman I incorporates Patel, which discloses using medicaments with more than one amine group for sustained drug release. DTX No. 253, Abstract; Tr. at 810:22-811:15 (Olejnik). Amine groups can accept protons at lower pH levels. DTX No. 253, at 10:1-18. For instance, medicaments containing multiple protonated amine groups can bond to polycarbophil and are "not completely available for release" into the eye when administered. *Id.* At a pH above 7.5, the amine groups for the most part do not become protonated, and "multiple amine-containing antibiotics unexpectedly exhibit enhanced sustained delivery over longer periods of time when compared to the same polymer systems used at a lower pH." *Id.* at 10:19-24. Tobramycin, an antibiotic with five amine groups, is Patel's preferred embodiment, *id.* at 4:63; Tr. at 736:18-20 (Hanes), and the patent states generally that "[sustained release] is observed with drugs that have more than one amine group." *Id.* at 10:1-9.

B. Conclusions of Law

i. Bowman I Renders the '999 Patent Obvious

Continuing with Bowman I, "in appropriate circumstances, a patent can be obvious in light of a single prior art reference if it would have been obvious to modify that reference to arrive at

the patented invention." *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016) (collecting cases). The "suggestion or motivation [to modify] may be derived from the prior art reference itself," *SIBIA*, 225 F.3d at 1356; *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988), a POSA's general or background knowledge, *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997) ("[T]he suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."), or the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996).

Bowman I discloses topical ophthalmic compositions comprising: (i) water soluble medicaments and polycarbophil; (ii) at pH of about 7.4 to about 8.5; (iii) at a viscosity of about 1,000 to about 3,400 cps; (iv) for treatment of inflammatory conditions of the mammalian eye. Tr. at 636:3-648:10 (Hanes). Based on the trial record, Claims 1, 3, 9, 10, 11, and 16 in the '999 Patent are obvious in light of Bowman I's disclosures. The chart below summarizes Defendants' *prima facie* evidence of obviousness.

Claim	'999 Patent	Bowman I
1	"[A] flowable crosslinked carboxy-containing polycarbophil mucoadhesive polymer." DTX No. 3, at 4:62-5:5.	Tr. at 636:13-637:1, 640:9-12, 641:1-5 (Hanes) ("Bowman I says particularly preferred polymers are lightly crosslinked acrylic acid polymers. Preferred commercially available polymers include polycarbophil, Noveon AA-1."); *id.* at 257:19-25 (Bowman) ("Q. . . . Now, in the Bowman I patent we looked at earlier, you also disclosed cross-linked acrylic acid polymers as flowable mucoadhesive polymers, right? A. Correct. Q. And your Bowman I patent also talked about the polycarbophil polymer known as Noveon AA-1, right? A. Correct."); *id.* at 305:1-6 (Bowman) ("Q. . . . Can you confirm that the – that your Bowman I example contained polycarbophils? A. That's what it says.").
1	"[W]herein the composition has a viscosity in the range of about 1,000 to about 3,400 cps." DTX No. 003, at 6:12-28, 8:50-9:35.	Tr. at 641:11-23 (Hanes) ("Q. Was there any discussion about viscosity in the specification of the Bowman I patent? A. Yes. The ophthalmic composition has a viscosity of 1,000 to 5,000 [cps]. A preferred viscosity range is 1,500 to 3,500 [cps].").

1	"[A] pH of about 7.4 to 8.5." DTX No. 003, at 6:29-34.	Tr. at 299:18-300:21 (Bowman) ("Typically, the pH of the composition [in Bowman I] will not be above 9.0, more preferably, not above 8.5 . . . . From this point of view, a pH towards 8.0 or higher is desirable . . . . In balancing a variety of factors overall, a preferred pH is from 7.0 to 7.8 . . . . And . . . when you're talking about a pH towards 8.0 or higher . . . that's describing an alkaline condition for the polycarbophil."); *id.* at 303:8-22 (Bowman) (describing a pH range from 7.0 to 7.8 for timolol, which is "in part" "[s]lightly alkaline"); *id.* at 640:15-17 (Hanes) ("[T]he pH is about 7.4 to 8.5, and in the abstract it says a pH of at least 6.7, but they also exemplified alkaline pH."); *id.* at 641:25-642:7 (Hanes) (further comparing pH in Bowman I to the '999 Patent).
3	"[W]herein the flowable mucoadhesive polymer is in an amount of about 0.5% to about 1.5% by weight of the composition." DTX No. 003, at 5:50-59.	Tr. at 642:17-20 (Hanes) ("[Claim 1 contains] .5 to 1.5 and so you can see, in Bowman I . . . that it contains .6 to .8 in a preferred embodiment of – polycarbophil.").
9	"[T]he viscosity of the composition is in the range of about 1,000 to about 2,000 cps." DTX No. 003, at 6:628.	Tr. at 302:12-20 (Bowman) ("Q. And, in fact, though, that viscosity range from 1,500 to 2,500 [in Bowman I], that was roughly the same viscosity range that you talked about in your '999 Patent, right? A. That's correct."); *id.* at 659:25-660:2 (Hanes).
10	"[W]herein the composition comprises from about 0.01 to 0.09 bromfenac by weight of the composition." DTX No. 003, at 3:30-30.	Tr. at 649:17-22, 660:3-5 (Hanes) (stating that Bowman I discloses ".005% to 2%" of its active ingredient); *id.* at 661:6-9 (Hanes) ("So, a [POSA] would be motivated to use those percentages because you could find support for that in Bowman [I] . . . for example, where they used .09% which is well within the range there.").
11	"[T]he composition has a pH of about 8.3." DTX No. 003, at 6:32-34.	Tr. at 642:23-25 (Hanes) ("Bowman I says typically the pH will not be above 9, more preferably not above 8.5."); *id.* at 299:18-301:13, 303:8-22 (Bowman); *supra*.
16	"[A]dministering the composition of claim 1 to the eye of a mammal in need thereof to threat inflammation of inflammatory conditions of the eye." DTX No. 003, at 1:7-10.	Tr. at 647:3-15 (Hanes) ("Bowman I talks about treating inflammatory conditions of the eye.").
16	"[T]he inflammatory condition is selected from the group consisting of	Tr. at 647:22-24 (Hanes) ("Q. Are there methods of use listed in Claim 19 that were associated with the FDA

	inflammatory conditions associated with [lengthy list of conditions]." DTX No. 003, at 2:12-15.	approved use of bromfenac? A. Oh, yeah. In 19, treatment of inflammation.").

ii. Plaintiffs' Counterarguments Are Unsuccessful

In response, Plaintiffs contend that Bowman I solves "entirely different problems, using entirely different active ingredients, [ ] from entirely different drug classes." Pl. Br., at 38. Plaintiffs also contend that Bowman I's teachings are unique to its preferred embodiment, timolol, because timolol has a high pKa, or charge when half of its molecules are in protonated form and half are in ionized form, and do not in fact disclose the claimed pH range in the '999 Patent. Plaintiffs finally argue that a POSA would not have been motivated to modify Bowman I to get the '999 Patent.

1. Bromfenac

Plaintiffs argue that Bowman I is not directed to bromfenac, since bromfenac is not named in the patent and was not FDA-approved at the time. Def. Br., at 37-38 (citing DTX No. 003, at 1:7-10). Plaintiffs also argue that Bowman I's "generalized disclosure" of "water soluble medicaments" is insufficient to teach a POSA anything about which specific drug compound to select to practice the formulation because "the scope of water-soluble medicaments is practically innumerable," Tr. at 793:17-20 (Olejnik), spanning many drug classes, each one of which "contains numerous species." *Id.* at 793:21-794:7 (Olejnik). According to Dr. Olejnik, Bowman I is so "exceptionally broad" that a POSA simply "wouldn't know where to go." *Id.* at 794:12-20 (Olejnik).

It is true that the word bromfenac is not in Bowman I "in black and white." *Id.* at 707:2-5 (Hanes); *id.* at 737:5-13 (Olejnik). But that far from settles the question whether a POSA would envisage using it based on the disclosures in Bowman I, coupled with relevant background

knowledge. *In re Wiggins*, 488 F.2d 538, 543 (Ct. Cl. 1973); *see also KSR*, 550 U.S. at 427-28 (emphasizing that the obviousness analysis is not conducted in "a narrow, rigid manner"). It also plainly "ignores the facts at issue in this case," *In re Gleave*, 560 F.3d 1331, 1337-38 (Fed. Cir. 2009), in light of which bromfenac would "come right to the mind of a POSA." Tr. at 648:8-22 (Hanes).

As an initial matter, Claim 1 in Bowman I discloses anti-inflammatories, NSAIDs, and ibuprofen specifically. DTX No. 003, at 3:13-16 (describing various "examples of water soluble medicaments for use in the present invention"); Tr. at 643:7-644:10 (Hanes). Bromfenac and ibuprofen are highly similar compounds. *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (en banc) (stating that similar properties can motivate using a non-named drug if the drug is "closely related to or suggested by a prior art compound"). Not only are they both anti-inflammatories, but they are water soluble, fat soluble, weak organic acid NSAIDs, with pKa values ranging from 4.29 (bromfenac) to 4.4 (ibuprofen), and log partition coefficients of at least 3.0 (bromfenac 3.22, ibuprofen 4.0). DTX No. 003, at 3:8-12, 3:53-58, 6:34-37. Claim 9 in Bowman I states that precisely these drugs—"lipophilic" ones with log partition coefficients "greater than 2.0, preferably greater than 3.0"—are "one form of the present invention." *Id.* at 3:53-56, 3:58-60. Thus, while Plaintiffs are correct that every asserted claim in the '999 Patent requires either "a therapeutically effective amount of bromfenac" or specific amounts of bromfenac (0.005% to 0.5% in Claim 4 or 0.01% to 0.09% in Claim 10), they are incorrect that Bowman I fails to suggest or disclose that compound simply because it is not one of the "only specifically mentioned drugs." *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1356 (Fed. Cir. 2016) (rejecting identical argument as to opioids).

What is more, when Dr. Bowman filed the '999 Patent in March 2009, the FDA had approved just five NSAIDs for use in topical ophthalmic solutions. Not only was bromfenac one, but it was "the darling" of the group because it had "highly effective anti-inflammatory activity," "rapid onset," and an "excellent safety profile," it "provide[d] sustained relief," it had been administered more than 10 million times successfully, it was "very low stinging," which patients could better tolerate, and doctors could dose it twice per day, which "makes it much more convenient" and is "a big motivation for a POSA" because the goal is always to "get to once per day," or a QD regimen. *Id.* at 630:25-633:25, 643:7-644:7, 636:12-19 (Hanes). In other words, bromfenac could "satisfy each ideal NSAID parameter." *Id.* at 630:25-631:12 (Hanes). This is highly "persuasive evidence" that a POSA would understand Bowman I to describe a formulation using bromfenac, even if that compound does not expressly appear in the text of the patent. *Purdue*, 811 F.3d at 1356 n.4 ("[That] two of the three sustained release drugs on that market at the time were opioids is persuasive evidence that a skilled artisan would understand McGinity as describing formulations that use opioids.").

More specifically still, a POSA seeking to modify Bowman I would begin by singling out NSAIDs as a class because they are named in Bowman I and are the best at inhibiting COX-2 enzymes, which are "the preferred enzyme[s] to inhibit for ocular pain inflammation," compared to other drug classes and even other anti-inflammatories. Tr. at 632:7-18 (Hanes). A POSA would also single out NSAIDs because Bowman I incorporates Patel, which lists all FDA-approved NSAIDs as potential active ingredients. *Id.* at 645:1-8 (Hanes); *id.* at 860:1-11 (Olejnik) (agreeing that, if updated as of March 2009, Patel's list would have included bromfenac). This is true even if Patel focuses on compounds with multiple amine groups, whereas bromfenac has just one amine group, because the patent recommends adding "anti-inflammatory agents selected from . . . the

FDA-approved topical NSAIDs" to its formulation. *Id.* at 653:20-654:7 (Hanes). From there, a POSA would single out bromfenac because it is "the most potent ophthalmic [drug] in inhibiting the COX-2 enzyme," so much so that it enables "twice daily dosing whereas all the other [by March 2009] were [still] three times or four times." *Id.* at 633:18-22 (Hanes); *id.* at 622:16-21 (Hanes) (flurbiprofen dosed 4x daily); *id.* at 623:15-19 (Hanes) (diclofenac dosed 4x daily); *id.* at 624:4-15 (Hanes) (ketorolac dosed 4x daily); *id.* at 625:15-20 (Hanes) (nepafenac dosed 3x daily). Bromfenac's potency is "12 times greater than that of indomethacin, 3.7 times greater than that of diclofenac, 6.5 times greater than amfenac, and 18 times [greater] than ketorolac." *Id.* (Hanes).

In other words, to a POSA in March 2009, there could be little doubt that bromfenac would apply in the Bowman I formulation. While Bowman I, of course, discloses "numerous" drug classes, including NSAIDs, immunomodulators, and other "classes of anti-inflammatory agents," *id.* at 795:3-797:15 (Olejnik); DTX No. 003, at 3:13-17 (naming "beta blockers such as timolol, levobunolol, betaxolol and atenolol; antibiotics such as tobramycin, anti-inflammatory agents such as ibuprofen; antivirals; and anesthetics"), and this led even Dr. Hanes to opine that Bowman I *per se* covers "almost every water soluble drug under the sun," *id.* at 639:7-17 (Hanes), a POSA would target a much narrower subset, focusing on bromfenac in particular, when reading Bowman I in context. NSAIDs were widely popular for ocular administration and bromfenac was the star compound among them. *Purdue*, 811 F.3d at 1356 ("[O]piods are a major class of analgesics and [ ] oxycodone was one of the most widely prescribed analgesics at the time.").

However wide "water soluble medicaments" may sweep in theory, then, it strains credulity to conclude that a POSA would not "at once envisage" bromfenac, or that a POSA would not reasonably expect that compound to be successful when practicing Bowman I. *Impax*, 468 F.3d at 1383; *In re Gleave*, 560 F.3d at 1337-38; *Purdue*, 811 F.3d at 1356; *Kennamental, Inc. v. Ingersoll*

Cutting Tool Co., 780 F.3d 1376, 1385 (Fed. Cir. 2015) (rejecting claim that there were too many prior art options for one in particular to be readily envisaged and holding that, because "a [POSA] would readily envisage the combination . . . , it would have been obvious"). This case presents a POSA who would have pursued "known options" from "a finite number of identified, predictable solutions." *KSR,* 550 U.S. at 421; *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006) (finding obviousness where prior art "expressly spelled out a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited class"); *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (finding obviousness when "a finite, and in the context of the art, small or easily traversed, number of options . . . would convince an ordinarily skilled artisan of obviousness"). It does not present a POSA who "merely throws metaphorical darts at a board" in hopes of arriving at a successful result, or a case where "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re Kubin*, 561 F.3d at 1359 (quoting *In re O'Farrell*, 853 F.2d at 903); *cf. In re Cyclobenzaprine*, 676 F.3d at 1070-73 (noting the "lack of a known PK/PD relationship for *any* formulation" in reversing district court's obviousness determination under clear error standard) (emphasis in original).

2. Properties of Timolol in Connection with pH

In contrast to their argument that Bowman I is too broad to disclose bromfenac, Plaintiffs insist that the patent is too narrow because it pertains to the precise pKa of its preferred medicament timolol, Tr. at 798:7-15, 801:13-802:13 (Olejnik), and it teaches about pH in that context only. *Id.* at 861:11-13 (Olejnik).

A drug's pKa refers to its pH when the drug is "half in protonated form and half in ionized form." *Id.* at 567:24-25 (Hanes); *id.* at 568:2-4 (Hanes) ("So if its pH is two units above, that means you have a hundredfold more ionized [particles] than you have with the proton on it."). Timolol has a pKa of 9.21 whereas bromfenac has a pKa of 4.29. *Id.* at 720:8-10 (Hanes). Based on this distinction, Dr. Bowman and Dr. Olejnik conclude, a person "looking at these references" would understand Bowman I's teachings to be specific to timolol because, "if you were to include bromfenac along [the same] lines, where you're increasing pH, you're actually creating a [more] ionized drug based on its pKa, so you're actually reducing its lipophilicity and you would have the opposite effect" compared to timolol. *Id.* at 813:6-15 (Olejnik); *id.* at 192:19-193:11 (Bowman) ("Q. . . . Does the ionization of a particular particle affect its ability to move across the eye and into the cornea? A. From the cornea back, yes, it does." . . . . Q. . . . Does the drug compound bromfenac demonstrate the same change in ionization or charge in relationship to pH levels that timolol demonstrates? A. No. It's totally different. Q. How so? A. Bromfenac is a carboxylic acid compound and at low pH it's more neutral. As you take the pH up it becomes more highly charged. So there, theoretically, as you get to higher charge, which means higher pH, it shouldn't permeate as well."). This is "one of those parameters that you would have to consider in determining how a drug would function in a particular formulation." *Id.* at 915:19-20 (Olejnik). The relationship between pKa and pH was first described in a paper by Paul Ashton, *id.* at 797:22-802:13 (Olejnik), titled "Formulation Influence on Conjunctival Penetration of Four Beta Blockers in the Pigmented Rabbit: A Comparison with Corneal Penetration." *Id.* at 799:1-3 (Olejnik); PTX No. 198. Ashton found that raising the pH of timolol makes its molecules "more neutral . . . more lipophilic, oil loving," so that "the apparent transport of the drug across the cornea" increases. Tr. at 800:7-22 (Olejnik). Bowman I incorporates Ashton's teaching on pH as it relates to timolol uptake. *Id.* at

801:13-18 (Olejnik). Dr. Bowman in turn insists that, because of bromfenac's lower pKa, it would not be obvious that it might permeate the cornea to the same degree as (or better than) timolol. *Id.* at 192:7-193:11 (Bowman).

Plaintiffs' evidence falls short here too. First, timolol is a preferred medicament only, not the only possible medicament, and a POSA would understand that difference. Dr. Olejnik recognizes as much: timolol is a "nonlimiting example," which merely "serves to illustrate certain features of the present invention." *Id.* at 860:12-861:10 (Olejnik); *id.* at 862:24-863:5 (Olejnik) ("Q. . . . And usually a statement of a preference doesn't mean that all others are excluded, true? A. To a certain extent, yes."). Same for Dr. Bowman. *Id.* at 639:2-5 (Bowman) ("Q. And when you read this particular disclosure in Bowman I, does it suggest that the entirety of the reference should be limited to just timolol? A. No."). Claim 1 discloses *many* drugs besides timolol, including "levobunolol, betaxolol, atenolol, it talks to antibiotics, anti-inflammatory agents, antivirals, and anesthetics," *id.* at 793:21-794:2 (Olejnik), and it does not "limit[] the description of the compositions to only those with timolol" in connection with discussing pH. *Id.* at 861:19-862:3 (Olejnik). Claim 9 further discloses any water soluble medicament that has a log partition coefficient of 2.0 or greater as a permissible active ingredient, which cannot reasonably be read to reference timolol only. *Id.* at 866:12-867:2 (Olejnik) (stating that bromfenac "certainly was known" as a water soluble medicament with a log partition coefficient as high as 3.0). In fact, as Dr. Olejnik agrees, "if Claim 1 was limited to timolol, there would be no need for Claim 9."[14] *Id.* at 866:15-23 (Olejnik).

Second, Dr. Bowman relied on articles about timolol to argue to the PTO how a POSA would expect bromfenac formulations to behave. JTX No. 2_350. Plaintiffs cannot now credibly

14 The doctrine of claim differentiation also requires the presumption that differences between claims are significant. *Tandon Corp. v. U.S. Int'l Trade Comm'n*, 831 F.2d 1017, 1023 (Fed. Cir. 1987).

assert that the compounds are entirely different or that a POSA could not possibly practice the invention in Bowman I with bromfenac. Third, and relatedly, Claim 5 in the '999 Patent combines bromfenac with an "additional therapeutically active agent" that includes a "glaucoma-treating agent" such as timolol. JTX No. 1, cl. 5. Perhaps most fatal, Bowman I discloses anti-inflammatories like ibuprofen in Claim 1, whose pKa is just 4.4, while bromfenac has a nearly identical pKa of 4.29, making it unreasonable to infer that Bowman I works strictly with high-pKa drugs. In light of this evidence, a POSA would not understand Bowman I to be limited to timolol or to drugs with high starting pKa's.

In any event, Plaintiffs overstate the apparent differences between bromfenac and timolol. Bromfenac is water soluble like timolol. Tr. 637:6-23, 639:23-640:8 (Hanes); 866:24-867:2 (Olejnik). It is lipophilic like timolol, which means that it tends to dissolve in fats. *Id.* at 340:4-12 (Bowman); *id.* at 637:25-638:17, 718:6-16 (Hanes); *id.* at 867:3-8 (Olejnik). It has a log partition coefficient of 3.22, higher than timolol's. *Id.* at 637:25-638:17, 718:14-16 (Hanes); *id.* at 867:3-8 (Olejnik). In fact, many drugs have a log partition coefficient greater than 2.0—which, while not dispositive proof that a POSA would select bromfenac from among them, certainly undermines Plaintiffs' contention that Bowman I contemplates timolol to the exclusion of *all* other compounds. *Id.* at 718:6-19 (Hanes). And it "was known prior to March 2009 that the pH where bromfenac was most soluble and stable in the bottle was . . . around 8.3," similar to timolol. *Id.* at 888:3-6 (Olejnik). As a result, bromfenac was one of just a few FDA-approved NSAIDs which *also met* Bowman I's lipophilicity, log partition coefficient, and pH specifications.

Third, I cannot find support in the record for Plaintiffs' suggestion that corneal "penetration is a function of a drug's pKa" alone. Plaintiffs emphasize this point because timolol has a higher pKa than bromfenac. When pH increases, bromfenac becomes more charged and less lipophilic,

whereas timolol becomes less charged and more lipophilic. *Id.* at 801:19-802:13, 813:5-15 (Olejnik); *id.* at 193:3-11, 339:6-22 (Bowman). Although these are technically different chemical mechanisms, the fact remains that bromfenac is still a lipophilic compound, and Bowman I requires only lipophilicity *in general*, not a specific lipophilicity threshold. *See, e.g.*, *id.* at 718:9-13 (Hanes) (stating that "Bowman I [simply] talks about using a water soluble medicament that is lipophilic and has a [certain] log partition coefficient"); DTX No. 003, at 3:53-56, 3:58-60 (providing that, "[g]enerally, one form of the present invention uses a water soluble medicament that is lipophilic and has a log partition coefficient of at least 2.0, preferably 3.0"); Tr. at 866:24-867:8 (Olejnik) (agreeing that bromfenac is lipophilic and water soluble even if its pKa value is lower than timolol's); *id.* at 383:3-18 (Olejnik) (explaining that the cornea's first layer "is the epithelium which . . . . prefers oily-loving compounds," and bromfenac "get[s] from the outside of the eye into the anterior chamber" in part because of its lipophilic qualities). Regardless, as Dr. Bowman testified, penetration depends on "a number of different factors," including but not limited to the "charge of the drug." *Id.* at 338:6-15 (Bowman) ("It has to do with a number of factors, not one factor."). This means that a POSA reading Bowman I would understand that corneal penetration can increase notwithstanding a high starting pKa, as is true for ibuprofen, which Bowman I *expressly* discloses. *See, e.g.*, *id.* at 863:16-23 (Olejnik) (admitting that Ashton, on which Bowman I relies, teaches that other drugs besides timolol increase corneal penetration as pH increases); *id.* at 853:17-854:13 (Olejnik) (writing in expert report that "even at a physiological pH, attachment [of polycarbophil] is firm enough to permit excellent retention of drug delivery system in the eye").

In sum, Bowman I indicates to a POSA that timolol can be substituted with other compounds without compromising the formulation, even if the pKa of the substituted drug is

somewhat lower than timolol's, and that the claimed pH levels in Bowman I are not specific to timolol's properties. *Cf. In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("A 'reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.'").

3. pH

Plaintiffs further assert that Bowman I does not disclose the pH range in the '999 Patent. DTX No. 003, at 3:38-52, 9:59-66, Fig. 1; Tr. at 800:11-22, 804:5-23 (Olejnik); *id.* at 719:9-20 (Hanes). This assertion contradicts a number of passages in Bowman I itself, all of which contemplate an alkaline or slightly alkaline pH, as well Plaintiffs' own trial testimony on the subject, which shows that polycarbophils can be effective in higher pH ranges based purely on the teachings in Bowman I. *Astra*, 222 F. Supp. 3d at 451 ("The term 'alkaline' standing on its own represents a concept that is well understood by those skilled in the arts of formulation and chemistry. It is fundamental chemistry that an 'alkaline' substance is a basic substance—a non-acidic, non-neutral compound having a pH greater than 7.").

To illustrate, Dr. Bowman testifies that Bowman I recommends "[s]lightly alkaline" pH ranges for timolol, *id.* at 303:19-22 (Bowman); discloses a pH range "not above 9.0" in general, "more preferably, not above 8.5, in view of the physiology of the eye," and "toward 8.0 or higher," which is "desirable," *id.* 299:18-23, 299:25-300:1 (Bowman); "describ[es] an alkaline condition for the polycarbophil when you're talking about a pH toward 8.0," *id.* at 300:10-21 (Bowman); and "contemplat[es] using [] polycarbophil polymers at a pH of 8.0 or above," *id.* at 301:10-13 (Bowman). Simply put, as Dr. Hanes testifies, Bowman I "shows that polycarbophil works . . . in essentially acidic and alkaline pH ranges." *Id.* at 674:10-12 (Hanes). Where "a technique has been used to improve" one product, such as a high pH in Bowman I, *id.* at 565:2-14 (Hanes), and a

POSA "would recognize that it would improve similar [products] in the same way," such as bromfenac plus polycarbophil, "using [that] technique is obvious." *KSR*, 550 U.S. at 417.

4. Problem to Be Solved

Next, Plaintiffs contend that Bowman I solves a different problem than the '999 Patent. According to Plaintiffs, Bowman I uses *sugar* to control release over time. DTX No. 003, at 2:40-47 ("None of the prior art teaches the use of a sugar as a medicament release profile enhancer."); *id.* at 9:57-65, Figs. 1-2 (containing examples showing that sugar can flatten release curve in a low viscosity formulation). By contrast, the '999 Patent "utilizes the enhanced *viscosity provided by polycarbophil* to drive additional drug across the cornea, resulting in increased delivery of bromfenac to the eye." Pl. Br., at 38 (emphasis added).

Plaintiffs begin by incorrectly defining the problem to be solved in the '999 Patent in terms of the '999 Patent's own invention. "In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention. Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). In much the same way, Plaintiffs miss the mark with respect to the problem to be solved in Bowman I: they narrowly define it by one feature that makes that patent novel in hindsight. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (holding that an overly narrow statement of the problem "[can] represent[ ] a form of prohibited reliance on hindsight, [because] [o]ften the inventive contribution lies in defining the problem in a new revelatory way"). In any event, Plaintiffs' position is misplaced because "[a] reference must be considered for everything it *teaches* by way of technology and is not limited to the particular *invention* it is describing and attempting to protect." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1076 (Fed. Cir. 2015)

(emphasis in original) (quoting *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985)); *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006) (holding that prior art reference "is not limited to the specific invention disclosed"); *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012). Thus, even assuming that Bowman I was intended primarily or solely to add sugar to improve sustained release, that in no way excludes the patent's other potential teachings.

Beyond that, the patents here solve similar problems. Bowman I's "object" is to provide an ophthalmic composition that has "a low viscosity and is easily administered in liquid drop form to the eye," has "a pH of greater than about 6.7," and contains a polycarbophil. DTX No. 003, at 2:1-8, 1:5-41; Tr. at 257:19-25, 305:1-307:2 (Bowman). Likewise, it is directed to "sustained release ophthalmic compositions that contain water soluble medicaments." *Id.* at 1:7-10; *id.* at 637:11-13 (Hanes). Likewise for the '999 Patent. JTX No. 001, at 1:25-27 ("[The] present invention provides topical ophthalmic formulations containing a non-steroidal anti-inflammatory agent, bromfenac, and a flowable mucoadhesive polymer); *id.* at 1:64-65 ("[T]he invention relates to a sustained release bromfenac delivery system."). In this sense, the '999 Patent essentially "'arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement." KSR, 550 U.S. at 417 (citations omitted); *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2013); *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1353-56 (Fed. Cir. 2013). Both Dr. Bowman and Dr. Olejnik testify to this point: (1) the '999 Patent does not exclude the use of a sugar but actually discloses it; (2) one formulation of the invention actually contains bromfenac, tobramycin, and polycarbophils, like Bowman I; and (3) other examples in the '999 Patent use Bowman I sugars in the same amounts as Bowman I suggests. Tr. at 894:9-897:25 (Olejnik); *id.* at 306:7-307:2 (Bowman). Accordingly, the problem to be solved is not a sound basis for declaring

the '999 Patent nonobvious. *Cf. Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019) (affirming "that a person of ordinary skill would not have [made proposed modification] to solve an undefined problem").[15]

5. Motivation

Finally, I reject Plaintiffs' argument that a POSA would not have been motivated to modify Bowman I to arrive at the claimed bromfenac formulation. Def. Br., at 37-39. To begin, as Dr. Hanes testifies, "your biggest motivation once there's a [twice daily] product is to get the first [once daily] product," and "bromfenac would give you the best chance of doing that, based on the prior art," *id.* at 652:7-13 (Hanes), given its potency compared to other compounds. *Id.* at 626:18-628:11 (Hanes). Further, Dr. Hanes points out, bromfenac was the active ingredient in Xibrom, a

15 To be sure, Dr. Bowman overemphasizes the importance of sugar to Bowman I. Dr. Bowman testifies that "Bowman I discloses a particular mechanism to get a sustained release . . . to take advantage of [the] ionization properties of timolol." *Id.* at 193:15-17 (Bowman). That mechanism is adding sorbitol, which "basically extend[s] the duration" of release time in the eye. *Id.* at 193:19-20 (Bowman); *id.* at 194:12-19 (Bowman) (stating that a formulation with sorbitol creates "a flatter curve and your drug delivery is – basically gets extended over a long period of time," whereas a formulation without sorbitol "goes very high . . . and comes back more rapidly to baseline, which means it has less sustained release"). Dr. Hanes testifies to the contrary: Bowman I does not disclose using sugar *alone* to achieve sustained release. Instead, "it's . . . . a combination of, you know, the composition with the polycarbophil." *Id.* at 670:9-23 (Hanes). I agree with Dr. Hanes. Dr. Bowman belies his own point by stating that, when developing the formulation in Bowman I, "we wanted a controlled release formulation and we found that if we used *polycarbophils* with sorbitol, we got slightly higher *viscosities* when you went from a *pH* of . . . 6.7 to 7.2 to 7.4, which i.e. translated into a longer sustained delivery." *Id.* at 195:7-11 (Bowman) (emphasis added). In fact, when asked if "*polycarbophil* was the sole reason" for the results in Bowman I, or whether it was "something more," Dr. Bowman answered: "It's really a *combination* of polycarbophil and the sorbitol." *Id.* at 195:21-196:1 (Bowman) (emphasis added). Even accepting that sugar confers some advantage, above and beyond all other ingredients, in controlling release time, *id.* at 805:9-13 (Olejnik) ("Bowman I concludes that Sample B containing no sorbitol is essentially not a sustained release composition, while Sample A, containing sorbitol, exhibits sustained release that is superior to [even] the more viscous/higher polymer content Samples C and D."), it is also true that "the presence or absence of the sugar, sorbitol, has *little effect* on the release profile in a high-viscosity environment." *Id.* at 803:21-23 (Olejnik) (emphasis added). That is consistent with evidence Dr. Bowman submitted to the PTO to support the '999 Patent, which showed that "after [he] took the sugar out of [his] bromfenac formulation, a bridging study confirmed that any differences between the two formulations were within normal biological variations." *Id.* at 309:10-15 (Bowman). Dr. Bowman informed the FDA of this fact. *Id.* at 309:16-17; *id.* at 898:21-899-3 (Olejnik) (stating that it is "correct" that "when the mannitol was removed and the buffering system was added, the nonclinical bridging study that was conducted demonstrated that the observed differences between the two formulations were within normal biological variations").

successful $200 million annual product, DTX No. 047_069, whose patent expired in 2009. Beyond that, of the five NSAIDs approved for ophthalmic use at the time, flurbiprofen and diclofenac had already been prepared with polycarbophil, rendering them unlikely drugs for improving Bowman I. *See, e.g.*, Tr. at 607:22-609:24 (Hanes); *id.* at 906:18-908:7 (Olejnik). And ketorolac and diclofenac produced discomfort and stinging, while nepafenac required shaking and higher levels of benzalkonium chloride exposure. *Id.* at 628:12-19 (Hanes). For these reasons, a POSA would have been motivated to choose bromfenac over any other available NSAID as Bowman I's "anti-inflammatory agent, such as ibuprofen."[16] *Id.* at 626:18-628:11 (Hanes).

Similarly, by March 2009, polycarbophil had achieved "worldwide approval" in "a wide variety of topical compositions," yet it had never been formulated with bromfenac. Xibrom, for instance, contained the polymer povidone, a much weaker mucoadhesive. According to Dr. Hanes, the prior art emphasized povidone as one of the worst polymers for adhesion and polycarbophil as "excellent" for that purpose, itself a motivation to use Xibrom's active drug in Bowman I's delivery system. *Id.* at 648:18-23, 887:19-22 (Hanes). Dr. Olejnik cannot disagree that one rationale for using polycarbophil is to increase residence time and slow down washout from blinking compared to other polymers. *Id.* at 376:21-377:3, 888:25-890:5 (Olejnik). Dr. Olejnik also cannot dispute that a POSA would have known about "improved performance" of polycarbophils, in particular a three-fold increase in concentration at the one-hour mark, in 2009. *Id.* at 875:7-22 (Olejnik); *id.* at 887:7-22 (Olejnik) (further admitting that he is not opining on whether a POSA would have sought to improve on the adhesive performance of povidone). Along these lines, InSite touted DuraSite as "a proven, patented synthetic polymer-based formulation

16 A POSA need only be motivated to pursue a suitable option, not the best option. *Par Pharm., Inc., v. TWI Pharm. Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014); *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013). Based on the trial record, it appears that bromfenac was the best option for topical eye solutions in 2009.

designed to extend the residence time of a drug relative to conventional topical therapies" and to work with a wide variety of compounds. DTX No. 454_4. Bowman I even discloses the polycarbophil Noveon AA-1, which the '999 Patent practices, *see, e.g.*, JTX No. 1, at 5:11; DTX No. 003, at 5:58-59, Ex. 1; Tr. at 257:23-25, 293:15-294:24 (Bowman); *id.* at 598:14-20 (Hanes), and which the PTO Examiner recognized as the "preferred commercially available polycarbophil polymer." Tr. at 257:15-18 (Bowman). Hence, a POSA in March 2009 would have been motivated to formulate bromfenac with polycarbophils, Noveon AA-1 in particular, to allow more drug into the eye over a longer period of time.

Next, by March 2009, numerous prior art references touted the utility of polycarbophils at a variety of pH ranges. *Id.* at 570:6-583:23 (Hanes) (reviewing six drugs); *id.* at 573:13-20 (Hanes); *id.* at 874:12-875:22 (Olejnik); *id.* at 575:10-576:9, 578:11-16 (Hanes); *id.* at 875:23-876:22 (Olejnik); *id.* at 578:17-583:23 (Hanes); *id.* at 583:25-586:20 (Hanes); *id.* at 586:21-589:14 (Hanes); *id.* at 589:20-594:15 (Hanes); *id.* at 607:22-609:24 (Hanes); *id.* at 876:24-880:18 (Olejnik); *id.* at 880:19-882:8 (Olejnik); *id.* at 882:10-883:22 (Olejnik). One of these was Bowman I, which taught a POSA that she could achieve higher corneal penetration at a higher pH, such as 8.0 or more. DTX No. 003, 6:29-38; Tr. 642:11-25 (Hanes).

If that were not enough, in 2007, patentees filed Sawa to create "[a]n eyedrop having an improved intraocular penetration and intraocular retention of medicaments," as "has been desired in the field of ophthalmology," using bromfenac, which is strong evidence that scientists working on topical ophthalmic formulations around the time of the '999 Patent believed it necessary to refine existing products and actively attempted to do so. *Id.* at 886:4-8, 886:23-887:2 (Olejnik) ("That was an inference."). Given everything a POSA knew about bromfenac, and with Bowman I's teachings on pH and polycarbophil in hand, I agree with Dr. Hanes that the formulation

disclosed in the '999 Patent is likely "the very first one[] that [the POSA would have] tried" to enhance residency time, increase corneal penetration, and achieve QD dosing. *Id.* at 653:12-13 (Hanes). The '999 Patent is obvious in light of Bowman I.

iii. Secondary Considerations of Nonobviousness Are Not Present

Even though I find the '999 Patent to be obvious, I must also analyze secondary considerations of non-obviousness. *KSR*, 550 U.S. at 415; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666 (Fed. Cir. 2000) ("[S]econdary considerations, when present, must be considered in determining obviousness."); *Cephalon, Inc. v. Slayback Pharma Limited Liab. Co.*, 456 F. Supp. 3d 594, 601-02 (D. Del. 2020) ("[T]he safer course for a district court faced with an obviousness challenge (and looking to avoid reversal by the Federal Circuit) is to treat *Graham*'s 'invitation' to look at secondary considerations like a subpoena."). My inquiry here "is not just a cumulative or confirmatory part of the obviousness calculus but [rather] constitutes independent evidence of nonobviousness," *Ortho-McNeil*, 520 F.3d at 1365, and is designed to "inoculate the obviousness analysis against hindsight." *Mintz*, 679 F.3d at 1378. A number of considerations may "give light to the circumstances surrounding the origin of the subject matter sought to be patented," including "commercial success, long felt but unsolved needs, [and] failure of others." *Graham*, 383 U.S. at 694. Still, "secondary considerations . . . do not necessarily control the obviousness conclusion," *Pfizer*, 480 F.3d at 1372 (citing *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988)), nor do they "always overcome a strong *prima facie* showing of obviousness." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) (citations omitted); *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion in this case that the secondary considerations cannot overcome the strong evidence of obviousness presented.").

Plaintiffs here rely on unexpected results. *See, e.g.*, Tr. at 851:13-852:6 (Olejnik). According to them, nothing suggests that "formulating bromfenac at 0.075% w/w in polycarbophil at the claimed pH and viscosity levels would deliver significantly increased levels of bromfenac to the aqueous humor faster than the closest prior art drug Xibrom™ (bromfenac ophthalmic solution) at 0.09%." Further, they contend, BromSite was the first ophthalmic NSAID to be approved by FDA for the *prevention* of ocular pain in patients undergoing cataract surgery. In their view, these "remarkable, unexpected results" are "highly probative of nonobviousness." *Lindemann Maschinenfabrik GMBH v. Am. Hoist and Derrick Co.*, 730 F.2d 1452, 1462 (Fed. Cir. 1984) (reversing obviousness finding where, although the claimed invention combined two prior art devices, the trial court overlooked "unexpected results nowhere suggested in the prior art").

1. Bromfenac Concentration Levels

The gist of Plaintiffs' first argument is that it was unexpected for the '999 Patent's lesser bromfenac concentration to be more efficacious than Xibrom. For support, Plaintiffs rely on rabbit studies, which compared penetration rate and residence time for a 0.09% bromfenac formulation and a 0.045% bromfenac formulation. Tr. at 817:1-8 (Olejnik). According to Plaintiffs, the studies showed that both formulations achieved higher maximum concentration ("C_{max}") and greater residence time ("T_{max}") than Xibrom's marketed product, whose concentration was 0.05%. *Id.* at 819:7-16 (Olejnik). Dr. Olejnik testified that a POSA would not have expected "any change in the bromfenac profile, simply because of the inherent properties of bromfenac itself." *Id.* at 820:22-24 (Olejnik).

This evidence fails to establish unexpected results on its own terms, as the very same studies showed that, while BromSite "resulted in proportionately more subjects with improvements in the primary endpoint versus [twice daily] Xibrom, the difference was not

statistically significant." *Id.* at 869:7-12 (Olejnik). Statistical significance is "a tool that's used by scientists to distinguish [ ] between those results that are real compared to those that are just random findings." *Id.* at 923:9-11 (Bloch). Dr. Bloch, whom I find credible, also reviewed the "preclinical and clinical studies that Dr. Olejnik commented on," *id.* at 918:18-19 (Bloch), opining that "the design of the [rabbit] study was flawed," "the statistical methods were also not correctly applied," and as such, "there are no differences in concentrations between [BromSite] and Xibrom at any time point." *Id.* at 928:2-6 (Bloch). As to design flaws, "the protocol did [not] specify a study outcome" nor did it "set forth how the [ ] study was to be conducted." *Id.* at 931:22-932:1, 934:9-12, 937:4-17 (Bloch). "[I]f you don't specify what you're going to actually analyze, then the sponsor [of the study] could just pick whatever outcome looks best and report on that." *Id.* at 938:22-24 (Bloch). One red flag associated with this here: the studies evaluated only some of the items specified in the original experiment design, raising the possibility that the sponsors cherry-picked favorable data. *Id.* at 938:15-20 (Bloch). In Dr. Bloch's estimation, "these deficiencies alone could invalidate the entire study results." *Id.* at 939:10-11 (Bloch). In thirty-plus years in the industry, Dr. Bloch could not remember "one instance where this [information] was not included" at the outset of a study. *Id.* at 939:17-23 (Bloch).

As to statistical methods, the studies used a paired t-test on a small sample size—five or six rabbits per group—even though the data were not normally distributed in a bell-shaped curve. *Id.* at 940:7-11 (Bloch). Dr. Bloch says that "a non-parametric test is required" in such a case. *Id.*; *id.* at 925:12-15 (Bloch) ("[I]f the sample size is small and the data are not normally distributed, then you can't use normal distribution theory to make statistical inferences . . . . you have to use other statistical methods."). According to Dr. Bloch, because the studies applied the wrong test, they generated "incorrect P values." *Id.* at 940:15-16 (Bloch). P values are important because they

measure the probability of obtaining the observed results and, therefore, determine whether a difference can be statistically significant. *Id.* at 924:1-15 (Bloch). The studies also "failed to adjust for multiple comparisons," *id.* at 940:19 (Bloch), meaning that they made an inference from 12 comparisons, six in each eye, about what would happen at the 24-hour mark, despite the fact that "there wasn't enough data to actually do an analysis" at that time point. *Id.* at 941:1-3 (Bloch). To this extent, the studies improperly "increased the chance of observing a correlation that is significant," *id.* at 641:6-21 (Bloch), and should have applied "a more stringent threshold of statistical significance than you would ordinarily apply." *Id.* at 942:6-8 (Bloch).

Dr. Bloch further testifies that the studies called for "the Wilcoxon signed rank test" instead of the paired t-test. *Id.* at 941:24-25, 942:11-13 (Bloch). Performing that test, Dr. Bloch found "no statistically significant differences between the Xibrom formulation and either .045 or .09 [% BromSite] formulations at any time point." *Id.* at 944:15-17 (Bloch). A P value of .05 is the "commonly accepted" threshold for statistical significance, yet "the smallest [ ] P value across all time points adjusted for multiple comparisons [was] .186," which is not "even close" to sufficient. *Id.* at 944:20-25 (Bloch). Because of this, "the scientists [conducting the rabbit studies and observing concentration quantities and residence time] cannot have sufficient confidence that the result is real." *Id.* at 945:3-4 (Bloch).

Finally, Dr. Bloch calls into question the C_{max} and T_{max} values reported in the studies. According to the studies, the BromSite 0.045% formulation reached its C_{max} at the half-hour mark and the 0.09% formulation at the one-hour mark, whereas Xibrom's 0.05% did not reach it until the two-hour mark. *Id.* at 946:17-25 (Bloch). Using the Wilcoxon 2 signed rank test, however, Dr. Bloch found "with 95 percent confidence, it's quite likely that actually . . . the T_{max} for Xibrom in the .045 group is at a half hour just like it was for the [other] concentration and then for the

comparison to the .09 [BromSite], again, . . . with 95 percent confidence, the true T_{max} could also be one hour." *Id.* at 949:1-7 (Bloch). Dr. Bloch made similar findings with respect to C_{max} values, which varied by up to an order of magnitude when they should have been "equal." *See, e.g.*, *id.* at 951:11-952:5 (Bloch). Plaintiffs do not attempt to rebut Dr. Bloch on any of these points or offer contrary testimony from their own statistical expert. Accordingly, I find that BromSite did not demonstrate unexpected results with respect to a lesser bromfenac concentration level.

2. BromSite's Indications and Usages

Plaintiffs' second argument is that BromSite demonstrated an unexpected result because it is indicated for the "prevention of ocular pain in patients undergoing cataract surgery," not merely for the treatment of pain. *Id.* at 828:22-23 (Olejnik). "All the other products that were available at the time . . . obtained approval just for postoperative inflammation after cataract surgery." *Id.* at 829:1-5, 834:4-15 (Olejnik). The difference between treating and preventing pain is "very distinct" in Dr. Olejnik's opinion. *Id.* at 845:21-23 (Olejnik).

To begin, underlying Plaintiffs' prevention indication is data they submitted to the FDA showing that about 80% of phase III clinical subjects treated with BromSite one day prior to surgery had no "VAS-assessed pain starting from post-surgery day one." *Id.* at 849:3-8 (Olejnik). The FDA's statistical reviewer considered a prevention indication "reasonable" on this basis. *Id.* at 850:6-7. Yet, at the same time, the reviewer observed "similar results for pain as a previously approved bromfenac ophthalmic solution which was also dosed one day before the surgery," and concluded that "there did not appear to be any *strong justification* for using the phrase prevention of ocular pain." *Id.* at 850:8-22 (Olejnik) (emphasis added). That alone is fatal to Plaintiffs' unexpected results theory.

In any event, results "must be shown to be unexpected compared with the closest prior art,"

Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 970 (Fed. Cir. 2006) (citation omitted), but Plaintiffs compared BromSite to a placebo only, not to Xibrom or any other NSAID. *Id.* at 953:24-954:1 (Bloch). And *of course* "it was expected that bromfenac [was] going to be better than a placebo." *Id.* at 848:16-19 (Olejnik). Plaintiffs likewise ignore the fact that Xibrom, Bromday, and Prolena all assessed the "proportion of subjects who achieved no pain at day one versus a placebo at day one" during their clinical trials, *id.* at 959:13-16 (Bloch), and Bromday and Prolensa were already administered one day prior to surgery when BromSite hit the market, while Xibrom was administered that way off-label. *Id.* at 874:4-11 (Olejnik).

Additionally, Dr. Bloch ran a product-by-product comparison of these drugs, concluding that BromSite did not generate any unexpected results with respect to pain prevention. For one, Dr. Bloch found that "a significantly higher proportion of subjects treated with [*each drug*] report[ed] having no pain at day one following surgery as compared to subjects treated with a placebo." *Id.* at 960:15-961:13 (Bloch). For another, he found that "at no time. . . was there a statistically significant difference between . . . BromSite and the other NSAIDs, excepting for the comparison of BromSite to Bromday," "the latter of which had a *higher* proportion of pain-free patients at day one than did BromSite." *Id.* at 962:5-8, 964:3-10 (Bloch). Xibrom prevented pain in 75.3% of patients compared to 78.9% for BromSite, a P value of .297, or a difference "likely due to chance," *id.* at 963:7-22 (Bloch); Bromday prevented pain in 6.8 percent *more* patients than BromSite, a P value of .037, *id.* at 964:3-10 (Bloch); and Prolensa prevented pain in 78.8% of patients, a P value of .98 or "almost 1," indicating essentially no difference at all. *Id.* at 964:21-24 (Bloch).

Plaintiffs respond that the "lack of a statistical difference in results does not necessarily mean that there is no difference in results." On this point, I agree. So, too, does Dr. Bloch, who

opines that "lack of significance doesn't mean that something isn't real," but only that "you haven't achieved the significance level required by scientists to be able to conclude that there is a real difference." *Id.* at 975:20-976:6 (Bloch). Plaintiffs then argue that patent law does not require statistical significance to find unexpected results. Even accepting that proposition as true, Plaintiffs must still demonstrate a "marked superiority" in their product, not a "mere difference in degree," which "is insufficient." *Bristol-Myers*, 752 F.3d at 977 (quoting *In re Papesch*, 315 F.2d 381, 392 (CCPA 1963)). Dr. Olejnik recognizes this important distinction, yet Plaintiffs fail to prove that it exists in this case. Tr. at 844:22-845:2 (Olejnik) ("I understand that to support a finding of unexpected results, those unexpected results must show a difference in kind rather than simply a difference in degree."). At best, Plaintiffs establish a marginal difference between BromSite and Xibrom, essentially no difference between BromSite and Prolensa, and an unfavorable difference between BromSite and Bromday. Since "the same behavior [is] observed in any [such] formulation, then there is no necessary nexus" between the claims in the '999 Patent and unexpected pain prevention.[17] *Kao*, 639 F.3d at 1069-70. Put another way, "[r]esults which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time," as here. *Galderma Lab'ys*, 737 F.3d at 739; *see also In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (finding increased efficacy, measured by percentages, to be a difference of degree and not of kind); *In re Budde*, 50 C.C.P.A. 1491, 319 F.2d 242, 246 (1963) (finding no unexpected results where ranges of reaction time and temperature constituted only a difference in degree rather than in kind); *In re Aller*, 42 C.C.P.A. 824, 220 F.2d 454, 456-57 (1955) (finding no unexpected results where improved yields over the

17 There is no evidence that any drug besides BromSite sought a pain prevention indication from the FDA, which perhaps explains why BromSite was the first to get that label. Tr. at 831:24-832:5; 833:7-834:15, 871:20-23 (Olejnik).

prior art, measured by percentages, reflect a difference in degree, not in kind).

When assessing unexpected results, I must instead evaluate "the significance and 'kind' of . . . results." *Bristol-Myers*, 752 F.3d at 977-78. The fact that BromSite prevents pain associated with cataract surgery better than *one drug* of three on the market, and only just barely, fails by definition to suffice as a difference in kind. *Compare In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (finding evidence that new drug was a *more* potent sedative and *stronger* anticholinergic effect than prior art insufficient to outweigh evidence of obviousness), *with In re Albrecht*, 514 F.2d 1389, 1396 (CCPA 1975) (reversing an obviousness rejection based on evidence of additional antiviral activity "totally dissimilar to any activity previously disclosed for prior art"); *see also Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected."); *In re Eli Lilly & Co.*, 902 F.2d 943, 948 (Fed. Cir. 1990) (finding claims obvious when "[patentee] has not shown that a significant aspect of his claimed invention is unexpected in light of the prior art"). Accordingly, I find that Plaintiffs have not demonstrated a secondary effect sufficient to overcome Defendants' *prima facie* evidence of obviousness. For all of the foregoing reasons, Defendants have successfully proved obviousness by clear and convincing evidence.

V. INVALIDITY – INEQUITABLE CONDUCT

Defendants finally argue that Dr. Bowman committed inequitable conduct by failing to disclose Bowman I to the PTO Examiner when prosecuting the '999 Patent. Inequitable conduct "is an equitable defense to patent infringement that, if proved, bars enforcement of a patent." *Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011) (en banc).

To prevail, an accused infringer must show that a patentee acted with specific intent to deceive the PTO. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1457, 1366 (Fed. Cir. 2008) (citing *Kingsdown Medical Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988)). "A finding that the misrepresentation or omission amounts to gross negligence or negligence under a 'should have known' standard" is not enough. *Therasense*, 649 F.3d at 1290 (citations omitted). "In a case involving nondisclosure of information," as here, "clear and convincing evidence must show that the applicant *made a deliberate decision* to withhold a *known* material reference." *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1181-82 (Fed. Cir. 1995) (emphasis added). "Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive." *Therasense*, 649 F.3d at 1290 (citing *Star*, 537 F.3d at 1366 ("[T]he fact that information later found material was not disclosed cannot, by itself, satisfy the deceptive intent element of inequitable conduct.")). Direct evidence of intent is "rare," so "a district court may infer [it] from indirect and circumstantial evidence." *Id.* at 1291; *Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1340 (Fed. Cir. 2009). Still, deception must be "the single most reasonable inference" in light of the evidence. *Therasense*, 649 F.3d at 1291; *Star*, 537 F.3d at 1366. This means that the evidence "must be sufficient to *require* a finding of deceitful intent." *Kingsdown*, 863 F.2d at 873 (emphasis added); *Scanner Techs. Corp. v. ICOS Vision Sys. Corp.*, 528 F.3d 1365, 1376 (Fed. Cir. 2008).

An accused infringer must also show that the information deliberately undisclosed is material, meaning that, with the information, the PTO "would have prevented [the] patent claim from issuing." *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1345 (Fed. Cir. 2013). After all, a patentee obtains no advantage from misconduct if the patent would have been approved in any event. *Keystone Driller Co. v. General Excavator Co.*, 290 U.S. 240, 245 (1933) ("The

equitable powers of the court can never be exerted in behalf of one . . . who by deceit or any unfair means has gained an advantage.") (emphasis added) (citations omitted).

But-for materiality "generally must be proved to satisfy the materiality prong," and "neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references in an affidavit constitutes affirmative egregious misconduct." *Therasense*, 649 F.3d at 1292-93. However, a party challenging a patent need not "strictly demonstrate but-for materiality in all cases." *Id.* "Where the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit," a court presumes materiality. *Id.*; *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571 (Fed. Cir. 1983) ("[T]here is no room to argue that submission of false affidavits is not material."); *Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1583 (Fed. Cir. 1996) ("Affidavits are inherently material."); *Outside the Box Innovations, LLC v. Travel Caddy, Inc.*, 695 F.3d 1285, 1294 (Fed. Cir. 2012) ("[A] false affidavit or declaration is per se material."). Materiality is presumed in this context because "a patentee is unlikely to go to great lengths to deceive the PTO with a falsehood unless it believes that falsehood will affect issuance of the patent." *Hazel-Atlas Glass Co. v. Hartford-Empire Co.*, 322 U.S. 238, 247 (1944).

Intent and materiality are, in turn, separate requirements. *Hoffmann-La Roche*, 323 F.3d at 1359. "A district court should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa." *Therasense*, 649 F.3d at 1290. Finally, the remedy for inequitable conduct is the "atomic bomb" of patent law. *Aventis Pharma S.A. v. Amphastar Pharm., Inc.*, 525 F.3d 1334, 1349 (Fed. Cir. 2008) (Rader, J., dissenting). Unlike validity defenses, which are claim-specific, 35 U.S.C. § 288, inequitable conduct renders the entire patent unenforceable, *Kingsdown*, 863 F.2d 877, and cannot be cured by reissue, *Aventis*, 525 F.3d at 1341, n.6, or reexamination. *Molins*, 48 F.3d at 1182; *Consol.*

Aluminum Corp. v. Foseco Int'l Ltd., 910 F.2d 804, 808-12 (Fed. Cir. 1990) (finding taint from inequitable conduct on one patent to spread to other patents in the same family).

Defendants in this case argue that Dr. Bowman committed inequitable conduct during prosecution by (i) failing to disclose Bowman I despite multiple inquiries from the PTO Examiner about whether the '999 Patent was obvious in light of two prior art references, the Sawa patent and the Roy patent; (ii) making misleading statements in his declaration on July 2, 2013, about Poloxamer 407; and (iii) making misleading statements in his declaration on April 7, 2014, about viscosity in the eye versus in the bottle, again in connection with Sawa and Roy. Tr. at 666:14-667:1 (Hanes).

A. Poloxamer 407

Dr. Bowman did not intend to deceive the PTO Examiner on the purpose/function of Poloxamer 407 in the '999 Patent. The PTO Examiner initially rejected the '999 Patent (in part) on the grounds that using Poloxamer 407, an excipient, to "increase permeation through the cornea" was obvious in light of publications on the topic. Tr. at 225:18-20 (Bowman); *id.* at 226:7-8 (Bowman) ("[T]he Examiner raised an objection that said Poloxamer would cause the permeability increase that we saw in the eye."). Dr. Bowman disputed the Examiner's conclusion, and the Examiner ultimately reversed course.

First, Dr. Bowman credibly believes—and explained then—that Poloxamer 407 affects drug uptake as "a function of its concentration." *Id.* at 225:14-227:5 (Bowman). According to Dr. Bowman, the literature showed that concentrations less than 1% are unlikely to impact uptake, whereas concentrations closer to 10% can. *See, e.g.*, *id.* at 225:22-226:3 (Bowman) ("The first one of the papers stated that it had to be around 10 percent before you get a – an effect where it affixed permeability through the cornea. Another paper which was made around 1 percent shows that it

made absolutely no difference. And from this, we determined that our formulation in this application was 0.2 percent should have no effect on the – affecting the permeability of the drug into the tissue."). The '999 Patent contains just 0.2% Poloxamer 407. PTX No. 017-A. Dr. Olejnik agrees with Dr. Bowman on the relationship between concentration and uptake, stating that he "would be surprised" if "Poloxamer 407 [could] have had an impact on the uptake of bromfenac at the kinds of concentrations that are being described in the '999 patent." Tr. at 839:23-840:1 (Olejnik); *id.* at 226:18-21 (Bowman) ("[The literature] showed that if you were at 10 percent, it would have an effect upon the permeation into the tissue. At 1 percent, it did not. Therefore, I concluded that at .2 percent it had no effect."). Dr. Hanes hardly testifies to the contrary. *See, e.g.*, *id.* at 684:1-10 (Hanes) (describing tests on rabbit corneas where 1.00% to 1.02% Poloxamer solution increased permeability compared to control group containing no Poloxamer).

Second, and in any case, Dr. Bowman credibly states that he added Poloxamer 407 to the '999 Patent in a very small amount to aid filtration during the manufacturing process—not to enhance uptake in the eye. *Id.* at 227:6-228:15 (Bowman). Indeed, "Poloxamer 407 is a – is a surfactant, and what it's meant to do is segregate molecules. What we did in this one is we had problems filtering bromfenac through the filler. That may have been because there was an interaction with bromfenac, it could have been a chelation, it could have been some other thing like crystallization or such . . . . So we added 407 to make it go through [the filter] earlier which has a mechanism of segregating molecules so they don't interact with itself and it'll go through the filter." *Id.* Without a filter to serve this purpose, "the concentration of bromfenac" in the formulation would "drop," compromising the drug's quality, efficacy, and integrity. *Id.* Dr. Hanes did not substantively contradict this testimony either, but rather agreed that it is "reasonable that

Poloxamer could help with filtering." *Id.* at 680:22-25, 680:24-681:4, 683:9-10, 607:14-21 (Hanes).

B. Viscosity/pH Data

Dr. Bowman also did not deceive the PTO Examiner when he stated in his 2013 declaration that the formulation in the '999 Patent would "behave differently" compared to Roy because of a different starting pH. The Examiner rejected the '999 Patent (in part) because Roy "suggests the same phenomenon that applicant has now observed." Tr. at 310:17-20. Specifically, "[t]he polymer will swell upon contact with tear fluid, which will cause gelation." *Id.* While Roy "discloses a preferred pH range, it is reasonable to expect that some degree of gelation would also occur at other pH values" upon contact with the eye, and "[a]pplicant was not presented any evidence to the contrary." *Id.* at 315:2-6.

In response, Dr. Bowman submitted his own viscosity data demonstrating that "a formulation containing polycarbophil at a pH higher than that of the eye behaves differently from formulations having a pH lower than that of the eye when applied to the surface of the eye." *Id.* at 315:7-9 (Bowman) ("The following information and study discussed below, which was conducted under my supervision, address[] this issue."). Because the formulation in Roy starts with an acid pH, and the formulation in the '999 Patent starts with an alkaline pH, the '999 Patent was not obvious in light of the Roy reference, nor was it obvious "to expect some degree of gelation . . . at these higher pH values for polycarbophils." *Id.* at 315:10-14 (Bowman). The Examiner issued the claims in part based on these representations, stating that "one skilled in the art would not have contemplated preparing a bromfenac containing ophthalmic composition comprising polycarbophil and having an alkaline pH." *Id.* at 324:2-8 (Bowman).

Defendants insist that Dr. Bowman "misled the Examine" by stating that "pH differences would [ ] change polycarbophils' gelation behavior." Def. Br., at 64. For evidence, they point to one of Dr. Bowman's papers, from 2009, where he performed a series of experiments showing that "[i]ncreases in the concentration of polycarbophil had the most significant effect on the viscosity of the solutions," while pH had a lesser—but still some—impact. DTX No. 7_3 (titled "Topical Polymeric Mucoadhesive Ocular Delivery System for Azithromycin"). It is unclear whether Defendants fault Dr. Bowman for not providing the data on polycarbophil, or for overstating the data regarding pH, but either way, their argument fails.

First, Defendants do not point to any falsehood which might render Dr. Bowman's declaration necessarily material or misleading. *Cf. Intellect Wireless, Inc. v. HTC Corp.*, 732 F.3d 1339, 1343 (Fed. Cir. 2013). Defendants, for instance, do not contend that pH in the bottle has *no* effect on viscosity in the eye. Nor could they, since Dr. Bowman's 2009 paper shows a correlation, as do the data Dr. Bowman submitted to the Examiner. *Id.* at 323:8-11 (Bowman) ("[A] small increase in pH raised the viscosity as well.") (referencing paper's findings). Dr. Hanes appears to acknowledge as much, stating that pH in the bottle "could increase [viscosity] a little bit" in the eye, which in the end is all that Dr. Bowman purported to show in his declaration. *Id.* at 569:24-25 (Hanes); *id.* at 567:2-9 (Hanes) ("As you increase the pH, . . . this causes [the carboxylic acids to become negatively charged and] swell really rapidly."). To that extent, "every statement in the declaration is a true statement," *Juicy Whip, Inc. v. Orange Bang, Inc.*, 292 F.3d 728, 744 (Fed. Cir. 2002), and Dr. Bowman did not "fail[] to submit a directly conflicting article [he] co-authored," *Pharmacia Corp. v. Par Pharmaceutical, Inc.*, 417 F.3d 1369, 1373 (Fed. Cir. 2005), contrary to Defendants' insistence.

Second, it is unclear why Dr. Bowman would have thought to inform the Examiner that a formulation's polycarbophil concentration *also* has an effect on viscosity, or "ha[s] the most significant effect," given that the Examiner raised a pH-specific objection and believed the '999 Patent to be obvious in light of Roy's teachings on *that* issue, and that the '999 Patent has "fixed concentrations" of polycarbophil. *Id.* at 323:14-19 (Bowman). Defendants certainly present no evidence that, but-for the information from Dr. Bowman's 2009 paper that polycarbophil concentrations affect viscosity *more than pH*, or *the most* of any factor, the Examiner would have declined to issue the claims. Hence, even accepting that Dr. Bowman misleadingly omitted his 2009 paper's teachings on polycarbophil, "the misleading part of the declaration was not material to the declaration or the application." *Juicy Whip*, 292 F.3d at 745 ("While the court is bothered by the Strattons' failure to correct the examiner's misunderstanding, the clarified identity of Boulahanis's employer was immaterial to the issue before the examiner."). As Defendants recognize, "[t]he pH you need to use to stabilize a drug in the bottle is not going to necessarily dictate the decision of whether or not you can also include a polycarbophil in the formulation," Tr. at 297:24-298:1, and as such, Dr. Bowman would not have thought to "go back and make sure that [he] had disclosed" the 2009 paper's data on the impact of polycarbophil concentration.

Third, Dr. Hanes testified that Dr. Bowman overstated the relationship between pH and viscosity when responding to the Examiner's obviousness rejection. Dr. Bowman informed the Examiner that a formulation "behaves differently" depending on pH, by which he meant that "viscosity differences" would be "significant and meaningful" depending on whether the formulation is basic or alkaline. *Id.* at 316:14-17 (Bowman). With a pH below that of the eye, "you're down to very close to the point where you will not get residence time," *id.* at 321:12-13 (Bowman), though there is not "a point at which you would not get increased residence time . . .

at all." *Id.* at 321:15-17 (Bowman). But Dr. Hanes' challenge on this point is unsupported by evidence: he offers no data or literature to dispute the viscosity measurements Dr. Bowman submitted to the Examiner to show that pH changes in the bottle cause even "significant and meaningful" viscosity changes in the eye. *Id.* at 752:24-753:11 (Hanes). The only publication to which Dr. Hanes points, the 2009 paper, more or less affirms Dr. Bowman's bottom-line conclusion that pH makes *some* difference. Dr. Hanes simply opines, with little explanation, that in his view, Dr. Bowman's measurements are not "really . . . significantly more viscous," *id.* at 685:21-686:19 (Hanes), and a formulation's starting pH would not be "materially different with respect to the goals of achieving sustained release," *id.* at 675:6-7 (Hanes), which does not rise to "clear and convincing evidence" of inequitable conduct. I therefore cannot conclude that it was misleading for Dr. Bowman to identify a difference in viscosity based on the pH level of a formulation in the bottle, even if it is *also* true that a formulation has increased residence time at pH levels within the claimed range in Roy. Essentially, Defendants argue that "[Roy] never said it would be *bad* to use DuraSite polymers at a pH in the range of 7.4 to 8.5," which does not suffice.[18] *Id.* at 297:15-17 (emphasis added).

C. Bowman I

i. Materiality

Finally, I turn to Bowman I. The PTO Examiner identified two prior art references, Sawa and Roy, in evaluating the '999 Patent. According to the Examiner, Sawa did not disclose "polycarbophil, the claim concentration, the claim viscosity, a sustained release formulation, or increased residence time," which all appear in the '999 Patent. Tr. at 668:1-3 (Hanes). To "fill

18 Further, "affirmative misrepresentations, in contrast to misleading omissions, are more likely to be regarded as material." *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1133 (Fed. Cir. 2006); *see also Hoffmann-La Roche*, 323 F.3d at 1367; *Rohm*, 722 F.2d at 1571.

those missing disclosures," the Examiner "cited Roy," and found the '999 Patent to be obvious in light of it. *Id.* at 671:14-19 (Hanes). Although "Sawa does not specifically disclose polycarbophil as the polymer . . . . Roy . . . discloses an ophthalmic composition of azithromycin that is useful in the treatment of bacterial infections of the eye," and "[t]he composition preferably includes likely crosslinked acrylic acid polymers as a flowable mucoadhesive polymer." *Id.* at 256:25-257:9. Further, Roy "include[s] the preferred commercially available polycarbophil polymer known as Noveon AA-1." *Id.* at 257:15-18.

Dr. Bowman responded that "Roy does not teach the use of bromfenac or polycarbophil." *Id.* at 672:2-3 (Hanes). Dr. Bowman also amended the '999 Patent to add a pH limit, distinguished Roy's polycarbophil formulations by stating that they involved a pH between 5 and 7, *id.* at 291:17-19; *id.* at 296:4-6, whereas the pH in the '999 Patent is "about 7.4 to 8.5," JTX No. 001, and concluded that "Roy teaches away from the presently claimed pH." Tr. at 297:11-13. Dr. Bowman participated personally in a phone call with the Examiner where he emphasized these differences. *Id.* at 312:6-11. Ultimately, the Examiner agreed with Dr. Bowman, writing that "the combination of Roy and Sawa [is] inappropriate because the pH ranges of the two references are different and incompatible." *Id.* at 313:7-10. The Examiner never reviewed Bowman I, however, which Defendants insist addresses every missing disclosure in Sawa/Roy.

At trial, Dr. Bowman argued that Bowman I is not material for more or less the same reasons as it does not render the '999 Patent obvious: it is directed to a different active drug (timolol), with a different goal (controlled sustained release over time), achieved through a different mechanism (addition of sorbitol), at a different pH range (preferably 6.7 pH, but anywhere from 5 to 7). *Id.* at 190:20-200:20, 336:2-341:8 (Bowman). Dr. Hanes disputes each point. *See, e.g.*, *id.* at 669:14-19, 669:21-25, 637:11-16, 669:24-670:4, 670:14-23 (Hanes). For the

reasons discussed with respect to obviousness, I find that Bowman I was material to the '999 Patent, and but-for Dr. Bowman's failure to disclosure it, the PTO Examiner would not have issued the claims. Basically the only difference between Bowman I and the '999 Patent is the active ingredient (bromfenac), which, while not listed *per se* in Bowman I, is readily contemplated/disclosed there. *See, e.g.*, *id.* at 797:16-21 (Olejnik) (seeming to acknowledge, at bottom, that the only element "missing" from Bowman I is bromfenac).

ii. Direct Evidence of Intent

Even if a prior art reference such as Bowman I is material in the sense of *Therasense*, a patentee must have specifically intended to hide it during prosecution to establish inequitable conduct. "While deceptive intent can be inferred from indirect and circumstantial evidence, that inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference able to be drawn from the evidence." *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1334 (Fed. Cir. 2011) (quotations and citation omitted) [hereinafter *Calcar I*].

Dr. Bowman testifies that he did not intend to mislead the Examiner at any point: he "would never do that." Tr. at 198:13-200:3, 224:25-225:11, 228:9-229:11, 232:2-11, 346:9-17 (Bowman). Dr. Bowman further testifies that he disclosed all information which he thought was relevant to the '999 Patent's claims. *Id.* at 349:14-18 (Bowman). Indeed, when asked at trial why he did not direct the PTO to Bowman I, Dr. Bowman said: "I considered the Bowman I totally different technology. It was a low pH with a different drug. The bromfenac patent was high pH with a different total structure drug . . . . So the two are opposites. Therefore, I didn't consider it the same technology." *Id.* at 198:18-199:3 (Bowman). Dr. Bowman, in short, did not see any relationship between Bowman I and the '999 Patent. *Id.* at 199:25-200:3 (Bowman). Even if I were to find Dr.

Bowman's testimony on this issue less than credible, that is insufficient to prove intent to deceive. *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 768 F.3d 1185, 1191 (Fed. Cir. 2014) ("[I]n light of *Therasense*, the finding of materiality and Mr. Obradovich's lack of credibility were insufficient grounds to find intent.") [hereinafter *Calcar II*].

iii. Circumstantial Evidence of Intent

In the absence of direct evidence of intent, Defendants rely on circumstantial evidence: InSite's profit motive to prosecute the '999 Patent, information Bausch and Lamb ("B&L") surfaced when considering whether to partner with InSite in 2009, discrepancies in what Dr. Bowman remembers about the B&L partnership, and discrepancies in the disclosures Dr. Bowman made to the FDA as opposed to the PTO.

1. Profit Motive

Insite "was down to a small bucket of products in development" at the time Dr. Bowman prosecuted the '999 Patent. *Id.* at 327:15-20 (Bowman). According to the company's 2009 Annual Report, its "future success" hinged on its "ability to obtain patents" and defend its "proprietary rights." *Id.* at 239:4-240:24 (Bowman); DTX No. 455_20-22. Dr. Bowman filed the '999 Patent around this time, *id.* at 240:25-241:2 (Bowman), when the "old Board got kicked off and a new Board came in," *id.* at 234:13-16 (Bowman), and the company was "highly dependent on [him]." *Id.* at 235:25-236:3 (Bowman) (quoting SEC filing) (further stating that company may have trouble "attract[ing] and retain[ing] key employees"). The '999 Patent "allowed [InSite] to cover three products that [it] had in development." *Id.* at 326:5-8 (Bowman). InSite sent out a press release to this end, asserting that the '999 Patent would encompass "all of our bromfenac product candidates." *Id.* at 315:18 (Bowman) (quoting release). The '999 Patent then issued in 2014—another critical date because, according to InSite's 2014 Annual Report, the company "face[d]

significant challenges relating to our lack of financial resources," which "will only enable us to continue our operations as currently planned until approximately May 2015." *Id.* at 327:21-328:5 (Bowman); DTX No. 86-6. The '999 Patent made InSite "a much more viable going concern." Tr. at 328:6-9 (Bowman).

Even so, I cannot find that the single most reasonable inference is that Dr. Bowman intended to deceive the PTO Examiner in an effort to save the struggling company. Many, if not most, drug companies substantially rely on patent prosecution for survival, and every patent is potentially a bet-the-company endeavor.[19] There is nothing suspect about that incentive or motivating factor here. Likewise, Dr. Bowman is certainly confident—to say the least—in his importance to InSite. *Id.* at 237:20-24 (Bowman) ("Q. . . . And that was a pretty weighty burden on your back wasn't it, Dr. Bowman? A. You want to be honest, no. I will be honest with you. Over the 30 years I worked there, it was the same way every day."). But the fact that Dr. Bowman knew—perhaps even overestimated—his value, by no means compels the inference that he intended to deceive the PTO into issuing the '999 Patent. *Cf. Kingsdown*, 863 F.2d at 873.

2. B&L Partnership

In 2009, InSite started "a dialogue with [B&L] about partnering on ISV-303," InSite's bromfenac product and the precursor to BromSite. Tr. at 243:11-14 (Bowman). In June 2010, while

19 *See, e.g.*, Bale Jr., Harvey E., *Patent Protection and Pharmaceutical Innovation*, 29 N.Y. Univ. J. Int'l L. & Pol. 95, 96 (1996) (describing the pharmaceutical industry as patent-intensive); Richard C. Levin, et al., *Appropriating the Returns for Industrial Research and Development*, Brookings Papers on Economic Activity 254, 269 (1987) (finding that the degree to which industry perceives patents as effective as "positively correlated with the increase in duplication costs and time associated with patents"); Edwin Mansfield, Mark Schwartz, & Samuel Wagner, *Imitation Costs and Patents: An Empirical Study*, Econ. J. 270 (Dec. 1981) (finding that patents in the pharmaceutical industry raise costs 40%, the highest of any market sector, strongly indicating that drug companies perceive patents as effective); Wendy H. Schacht & John R. Thomas, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984*, CRS Report for Congress 1, 2-5 (Jan. 2005) (describing important role of patents in pharmaceutical innovation).

conducting due diligence, B&L asked whether InSite had patent protection on ISV-303 and requested all patent application numbers and related information. *Id.* at 243:19-244-2 (Bowman). B&L then wrote to InSite's patent attorney, "[Dr. Bowman] has stated that he has all of this information." *Id.* at 244:5-6. After further due diligence, based in part on what Dr. Bowman provided and on its own searches, B&L posed the question: "Why do you believe that the ['999] Patent is not obvious? It's been shown that combining other drugs with DuraSite gives higher exposure. So it seems obvious that combining bromfenac with DuraSite would lead to greater exposure. What are your claims that are nonobvious[]?" While Dr. Bowman received this correspondence, it is unclear who passed it along to him or in what context, and he does not remember whether he responded. *Id.* at 247:2 (Bowman). Dr. Bowman also does not remember what information he provided to B&L to answer their initial query for materials related to patentability, the implication being that he cannot recall if he provided Bowman I.

Dr. Bowman certainly attempts to distance himself from B&L's inquiries. He purports to scarcely remember the dialogue at all, even though B&L requested patent protection for ISV-303, stated that Dr. Bowman had the information they needed, presumably received whatever materials he had, asked about obviousness in light of prior art, and presumably disclosed the references it gathered in its own search. Moreover, when confronted with these facts, Dr. Bowman's demeanor was evasive, borderline flippant. I nevertheless cannot conclude that the single most reasonable inference from his testimony is that he intended to deceive the PTO Examiner, even though I find his answers less than credible. *Therasense*, 649 F.3d at 1291; *Star*, 537 F.3d at 1366. There simply is no evidence as to what prior art references Dr. Bowman sent to B&L in 2009-10 or what references B&L sent to him in return. Defendants can only surmise that either Dr. Bowman or B&L disclosed Bowman I during due diligence, which falls short of clearly and convincingly

proving deceptive conduct a few years later, when Dr. Bowman did not disclose Bowman I to the PTO.

3. Dr. Bowman's Memory

Next, and relatedly, Defendants point out that Dr. Bowman cannot remember what he provided to B&L or what B&L provided to him in 2009-10, or whether he responded to their obviousness questions at all, but "recalls with impressive detail" InSite's bromfenac work from the same time period. *Id.* at 244:3-13, 246:4-10 (Bowman). Defendants then cite *TransWeb, LLC v. 3M Innovative Properties Co.*, 16 F. Supp. 3d 385 (D.N.J. 2014), for the proposition that when a witness "recall[s] with impressive detail certain aspects" about a series of events, but "professe[s] not to remember any details" about other aspects of that same event, the witness is not credible, intends to deceive, and commits inequitable conduct. *Id.* at 399-400. But *TransWeb* is inapposite. There, the event the witness recalled in detail and the event about which he pretended not to know at trial were one and the same: an Expo at which the witness obtained samples of a competitor's product, but which he never disclosed to the PTO. 16 F. Supp. 3d at 398. By contrast, here, Defendants compare proverbial apples to oranges: Dr. Bowman's laboratory work developing bromfenac products with InSite (which he remembers) and his responses (if any) to B&L's inquiries about obviousness in the context of a prospective business partnership (which he has apparently forgotten). It is too attenuated to use Dr. Bowman's knowledge about the former to infer intent to deceive on the latter.

4. Dr. Bowman's FDA Disclosures

Finally, Defendants argue that Dr. Bowman submitted different disclosures to the FDA and the PTO about the Roy reference. In the BromSite NDA, Dr. Bowman informed the FDA that he performed "five separate viscosity measurements . . . to an Azasite product containing 1%

azithromycin" in 2006 as part of "method validation work" and "method ruggedness" analysis. Tr. at 259:23-261:8 (Bowman). These tests involved "DuraSite vehicle[s]." *Id.* Dr. Bowman then told the FDA that "[a]ll inactive excipients used in ISV-303 have been used in the FDA-approved AzaSite, azithromycin, 1 percent ophthalmic solution," including polycarbophil. *Id.* at 284:13-17 (Bowman); *id.* at 286:13-18 (Bowman) ("All excipients used in ISV-303 have a history of use in pharmaceutical products."). Dr. Bowman further stated that "[p]olycarbophil, CAS-9003-97-B, also known as Noveon AA-1, is a mucoadhesive agent and has been used in various applications including ophthalmic solutions." *Id.* at 287:6-11 (Bowman).

Yet, before the PTO, Dr. Bowman emphasized that each DuraSite formulation is tailored to the specific active drug in the formulation, *id.* at 285:18-21, and that it was not obvious to combine bromfenac with the ingredients in AzaSite. *Id.* at 286:4-7, 286:8-12 (Bowman) ("Q. . . . Well, you didn't tell the FDA that you had any concerns about combining bromfenac with the same list of inactive excipients that you had previously used with your azithromycin product, right? A. We didn't state that."). Likewise, Dr. Bowman told the PTO that there was "a significant difference" in the viscosities at the pH ranges he tested with respect to the '999 Patent, *id.* at 317:23-318:3 (Bowman), but he told the FDA that the still wider viscosity range in the "release specification" for BromSite was permissible. *Id.* at 221:21-25 (Bowman).

From this, Defendants conclude, when "an official of [a company], who was involved in both the FDA and PTO submissions, chose to disclose" one thing "to the FDA, but not to the PTO," that "certainly supports a finding of deceptive intent to withhold the disclosure from the PTO." *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005). The first flaw in Defendants' position is that, in *Bruno*, the Federal Circuit inferred intent from "the high materiality" of the nondisclosed prior art, a "sliding scale" which is no longer

acceptable under *Therasense*, where the court established "a revised and narrower test for inequitable conduct." *Calcar II*, 768 F.3d at 1188. It is no longer the case that, "[w]hen balanced against high materiality, the showing of intent can be proportionally less." *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1381 (Fed. Cir. 2001). Hence *Bruno* does not move the needle toward finding intent to deceive. Second, FDA and PTO disclosures serve very different purposes, and Defendants have not presented evidence to suggest that they must or should overlap in this case. A patent prosecution concerns originality and innovation, whereas an NDA concerns safety and efficacy, and as such, it is plausible that a pH, viscosity, or excipient difference would be critical in the FDA's estimation but immaterial in the PTO's. *Accord Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1367 (Fed. Cir. 2003) ("Intent to deceive cannot be inferred simply from the decision to withhold the reference where the reasons given for the withholding are plausible.").

Third, and most critically, Dr. Bowman did not disclose Bowman I to *either* agency. Dr. Bowman instead made representations about Roy to the FDA, which the PTO Examiner had already investigated. Had Dr. Bowman selectively disclosed *Bowman I*, this may well be a different case. *Cf. Merck & Co. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989) (ruling that inference of deceptive intent was supported by "damning" evidence, including that applicant submitted material information to FDA on "amitriptyline data" while simultaneously withholding *the same* from PTO, and attempts to explain the disparity "strain[ed] credulity").

In sum, Dr. Bowman should have disclosed Bowman I, which was material to the '999 Patent's claims. It was negligent, possibly grossly negligent, not to do so. Some of Dr. Bowman's testimony on this subject also falls far short of credible. Yet, none of that is sufficient to clearly and convincingly establish specific intent to deceive the PTO. *Therasense*, 649 F.3d at 1285. In

this Court's view, having heard Dr. Bowman testify and observed his demeanor throughout trial, an alternative explanation for his nondisclosure jumps out: hubris. Dr. Bowman was simply too confident in his own opinion to believe that anyone could see the relevance of Bowman I any differently than he saw it, and he was not accustomed to justifying his actions to others or to facing challenges on topics related to his expertise. That much he conveys in his testimony, both in his answers and his manner and tone. But the fact remains that such a disposition or attitude, problematic though it may be, does not support a finding of specific intent as the Federal Circuit defines it. *Scanner*, 528 F.3d at 1376 ("Whenever evidence proffered to show either materiality or intent is susceptible of multiple reasonable inferences, a district court clearly errs in overlooking one inference in favor of another equally reasonable inference."). Defendants thus have not demonstrated inequitable conduct by clear and convincing evidence.

VI. CONCLUSION

For the foregoing reasons, I find that: (1) Defendants' generic product does not literally infringe the '999 Patent; (2) Dr. Bowman did not engage in inequitable conduct when he failed to disclose Bowman I to the PTO Examiner, because he did not specifically intend to deceive the Examiner even though Bowman I was material; (3) Claims 1, 3, 9, 10, 11, and 16 in the '999 Patent are obvious in light of Bowman I; and (4) the claim terms mentioning viscosity are indefinite. Accordingly, I hold that the '999 Patent is invalid. An appropriate Order follows.

DATED: September 30, 2021

/s/ Freda L. Wolfson
Hon. Freda L. Wolfson
U.S. Chief District Judge